An assessment of two novel tools for advanced haemodynamic monitoring in critically ill children

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An assessment of two novel tools for advanced haemodynamic monitoring in critically ill children

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Declaration

I confirm that the work presented in the thesis is original and my own. All the references are cited accurately and appropriately to the best of my knowledge.

Abstract

Background

Critically ill children require accurate haemodynamic assessment to evaluate the severity of illness or response to therapy. Clinical estimation of cardiac output is inaccurate. Hence, advanced haemodynamic monitoring devices may help guide physicians towards the most appropriate treatment strategy. However, none of the currently available monitors for children fulfil all the criteria of an ideal device.

Methods

We evaluated two novel minimally invasive haemodynamic monitoring devices in 100 critically ill children. The transpulmonary ultrasound dilution (TPUD) method is a validated indicator dilution based technique for measuring cardiac output in children. Pressure recording analytical method (PRAM) is an arterial pulse contour based method and is not yet validated in children. We compared PRAM with TPUD both in terms of agreement with absolute values of CO and also quantified the ability of PRAM to track changes in CO in response to therapy. We also evaluated the ability of TPUD to identify, and quantify, small anatomic shunts. Finally, a range of variables measured by TPUD and PRAM were assessed for their ability to predict response to fluid bolus administration. The contribution of baseline myocardial contractility towards that response was also evaluated.

Results

PRAM showed unacceptable level of error for estimation of absolute values of CO and was unable to accurately track changes in CO. TPUD could identify small anatomic shunts. All of the volumetric variables were unable to predict accurately for fluid responsiveness. Myocardial contractility was found to be an important determinant of the response of stroke volume to fluid bolus administration.

Conclusion

A revision of the current algorithm of PRAM is recommended for measurement of CO in children. The predictive ability of the studied variables was poor to moderate for determining response of stroke volume to fluid bolus administration.

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The thesis is dedicated to my wife Meenakshi, daughters - Pari and Rhea and my parents. It would not be possible to complete this research without their moral support.

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List of abbreviations

ACVI	Active circulating volume index
CBVI	Central blood volume index
CI	Cardiac index
Conf. intv.	Confidence interval
CO	Cardiac output
ECG	Electrocardiogram
ICG	Indocyanine green
LV	Left ventricle
LVEDA	Left ventricular end diastolic volume
PAC	Pulmonary artery catheter
PICU	Paediatric intensive care unit
PRAM	Pressure related analytical method
PCM	Pulse contour method
ΔPOP	Change in pulse oximetry plethysmography
PPV	Pulse pressure variation
PVI	Perfusion variability index
PWTT	Pulse wave transit time
ROC	Receiver operating characteristic
RV	Right ventricle
SV	Stroke volume
SPV	Systolic pressure variation
SVV	Stroke volume variation
TEB	Thoracic electrical bioimpedance
TEDVI	Total end diastolic volume index
TOE	Transoesophageal echocardiography
TPLD	Transpulmonary Lithium dilution
TPTD	Transpulmonary thermodilution
TPUD	Transpulmonary ultrasound dilution technique
WBEB	Whole body electrical bioimpedance

Preview

What this thesis aims to add

Advanced haemodynamic monitoring is an important adjunct in the management of critically ill children. Broadly speaking, this includes assessment of adequacy of the balance between oxygen delivery and consumption. A key component of oxygen delivery is cardiac output, which must also include consideration of the inter-related variables comprising cardiac output (preload, afterload, contractility and diastolic function). To date, bedside measurement of cardiac output in children has been hindered by invasiveness of devices; however the past decade has seen more widespread uptake due to the introduction of less invasive techniques. However, it is vital that new techniques are evaluated adequately. One of the commonest therapies for improving oxygen delivery is fluid bolus administration; however this is not without risk, as fluid overload is increasingly recognised as a risk factor for poor outcome. Thus, a tool to predict fluid responsiveness may obviate the need for unnecessary fluid administration.

My thesis aims to explore aspects of the above in critically ill children, via evaluation of two novel tools for advanced haemodynamic monitoring. Specifically this will include:

(i) Validation of accuracy of cardiac output measurement using a semi-invasive, pulse-contour based device: Pressure Recording Analytical Method (PRAM)

(ii) A systematic evaluation of fluid responsiveness using variables measured by PRAM and also a dilution based technique (transpulmonary ultrasound dilution, TPUD). This will include quantification of the predictive ability (in terms of stroke volume change), of various static and dynamic variables from the two devices, followed by quantification of the effect of baseline contractility on prediction.

(iii) Determination of the accuracy of TPUD for detection of anatomic shunts. This is because anatomic shunts may impact on clinical status; and may go undetected in settings where echocardiography is not readily available.

The thesis is presented in 2 parts.

Part A: Consists of an overview of haemodynamic monitoring with reference to paediatric applications.

Chapter 1 is an introduction to advanced haemodynamic monitoring, with emphasis on methods for measurement of cardiac output.

Chapter 2 is a summary of static and dynamic variables estimating preload and fluid responsiveness.

Chapter 3 is a detailed description of TPUD and PRAM technology

Part B: Describes our evaluation of TPUD and PRAM in 100 critically ill children.

Chapter 4 Methodology and study protocol

Chapter 5 is a validation study of the accuracy of cardiac output measurement using PRAM with TPUD as the reference method (TPUD has been evaluated previously). This included both absolute accuracy and trending ability.

Chapter 6 is a systematic evaluation of the predictive ability (in terms of stroke volume change), of various static (TEDVI, ACVI and CBVI) and dynamic (SVV, PPV and SPV) variables measured using the two devices. I also investigated the influence of baseline contractility on relative stroke volume changes following fluid bolus administration.

Chapter 7 is an observational study assessing the accuracy of TPUD technology for detection and quantification of small anatomic shunts with Doppler echocardiography as the reference method.

Chapter 8 is the summary of the major findings from our study, including a discussion of the implications and relevant literature. Finally, I provide suggestions for future research in the field of paediatric advanced haemodynamic monitoring.

APPENDIX

- Patient and parent information leaflet
- Consent form

PART A

Chapter 1 General principles of monitoring in intensive care and review of cardiac output monitoring

1.1 Introduction to CO monitoring

A key facet of management of critically ill patients is provision of adequate tissue perfusion and oxygen delivery.[1,2] Oxygen delivery is directly dependent upon cardiac output as shown by the relationship below:

$$Oxygen\ delivery = Oxygen\ content\ of\ arterial\ blood \times Cardiac\ output$$

Cardiac output is defined as the volume of blood ejected by heart in one minute. It is usually expressed in relation to body surface area. The normal value in paediatric age range is 3.5 – 5.5 l/min/m^2 .[3] Clinical estimation of cardiac output is challenging, even amongst experienced clinicians. Tibby et al evaluated the ability of clinicians involved in the provision of paediatric intensive care for estimation of cardiac index in ventilated children, based upon physical examination, clinical and bedside laboratory data. They demonstrated a poor correlation both categorically (kappa statistic 0.09, weighted kappa 0.17) and numerically (r = 0.24, 95% conf. intv 0.06 to 0.41).[4]

Hence, pathological states resulting in inadequate delivery of oxygen such as shock, require accurate estimation of cardiac output. This facilitates provision of targeted therapy towards set treatment goals during management of critically ill patients. The use of cardiac output monitoring in fluid refractory shock is further recommended by the International consensus conference of 'haemodynamic monitoring in shock and implications for management'.[5]

A range of techniques is available for measuring CO. They can be classified as utilizing the Fick principle, indicator dilution, Doppler ultrasound, pulse contour analysis, impedance, and other miscellaneous methods.

When considering the evaluation of these techniques, certain characteristics mentioned below should be considered to justify their use and cost effectiveness[6]:

a) Tests should be accurate and responsive

Monitoring tests should accurately reflect the true value of the entity measured and be responsive to capture the changes following various interventions or with spontaneous changes in a patient's clinical condition.

(b) Monitoring test should improve patient outcome measures by guiding therapy

Monitoring is performed with an aim to check disease progression and measure the effect of various interventions to improve patient outcomes. This may hold true for most methods or tests but the use of pulmonary artery catheters (PAC) for CO monitoring did not improve mortality rates among patients. CO monitoring using Pulmonary artery catheters came into existence in 1970's. Most studies failed to show any improvement in the mortality rates with the use of these devices. A multi-centre study by Connors et al included approximately 6000 adult patients undergoing PAC monitoring[7]. They reported an increase in mortality, length of stay and cost in patients with PAC in situ as compared to the matched controls without PAC. Another RCT with approximately 1000 adult patients reported a complication rate of approximately 10%[8]. These results are partly attributed to:

(i) Lack of knowledge to optimally use PAC and interpretation of the obtained data. Iberti et al demonstrated a mean test score of 65% in a questionnaire based survey to approximately 500 physicians, assessing their knowledge and understanding of the use of the pulmonary artery catheter and interpretation of data derived from it [9].

(ii) Absence of treatment algorithms and management protocols linked to CO monitoring may have also contributed to failure of these devices in improving patient outcomes. Gan et al followed a treatment algorithm based upon stroke volume and FTc estimation in mixed surgical adult patients using oesophageal Doppler monitoring devices for CO estimation. They reported benefits in reducing the duration of hospital stay and incidence of feed intolerance[10]. Sinclair et al reported similar results with their use of clinical algorithm related to trans oesophageal Doppler[11]. In view of the current evidence showing a reduction in incidence of central venous

line insertion, length of stay, readmissions or repeat surgery and an estimated cost saving of £1100/patient, National institute for health and care excellence UK, has recommended the use of esophageal Doppler in adult patients undergoing major or high risk surgery [12].

(c) Clinical validity

Most of the CO monitoring devices mentioned have been studied and validated in adults and extrapolation of data towards paediatric age group may not always be the correct approach. Only a few devices or techniques are validated for measurement of CO in paediatric practice. Pulmonary artery catheter and Transpulmonary thermodilution methods are long been regarded as benchmark methods in clinical practise. One of the devices used in our study is based upon indicator dilution method and is validated against PAC in paediatric patients.

(d) Signal to noise ratio

Signal is the meaningful change in biological value measured over a given time. Noise is the background short term measurement variability arising as a result of biological or technical reasons. An ideal monitoring test should have a large signal to noise ratio and should be able to differentiate meaningful change from usual biological or technical variability. This is important to reduce bias in the measurements. There are various ways to reduce the background noise and hence improve the accuracy of CO assessment. Firstly, choosing devices with low coefficient of variation can reduce technical component of the noise. Both the monitoring devices in our study had coefficient of variation of less than 10%. Secondly, we took mean of multiple CO measurements both before and after the intervention to help reduce the background noise [13].

Shepard et al also described desirable properties of an ideal CO monitoring device. They included no morbidity (invasiveness), continuous use, rapid response time, operator independence reproducibility, accuracy and cost effectiveness.[14]

Paediatric practice presents a range of unique challenges for CO monitoring, including: patient size, anatomical variants, anatomical shunts, etc.

This chapter provides an overview of different cardiac output (CO) monitoring devices available along with their limitations, sources of errors and applicability in paediatric practice wherever possible.

The chapter also gives a representative summary of paediatric studies comparing different CO monitoring devices using bias and precision statistics (wherever data is available). As such, it is presented as a narrative, rather than systematic review.

A narrative review of adult and animal studies for different CO monitoring devices is provided collectively at the end of the chapter to provide reader an insight into the relevant literature. This list is not a systematic review or exhaustive in nature.

The appropriate statistical method for demonstrating agreement between the two methods (experimental and reference methods) for measuring CO is Bland Altman analysis.[15] Bias is defined as the mean difference between the two methods. Limits of agreement are calculated as mean bias $\pm$ 1.96 Standard deviation (SD) of the bias. Percentage error is calculated as (1.96 SD of bias / mean CO of the reference method). An acceptable percentage error is typically defined using two considerations: (a) the precision of the reference method, and (b) that the new method should be at least as accurate as the reference. Using a standard statistical approach for combining variance, and taking pulmonary artery thermodilution as a reference, Critchley defined an acceptable percentage error of $\pm$ 30%[16]

1.2 Methods for estimation of cardiac output

1.2.1 Fick method

(i) Direct Fick Method

CO estimation first described by Adolf Fick in 1870 has long been been considered a laboratory gold standard. It involves adding or removing an indicator and measuring the change in indicator concentration upstream and downstream of the point of indicator addition or removal (fig 1-1).[17] The most commonly employed indicator is oxygen (consumption) [carbondi-oxide (production) may also be used]. CO is calculated by the following formula:

$$CO = \frac{VO_2}{CaortaO_2 - Cmixed\ venousO_2}$$

where
CO: cardiac output
VO_2: oxygen consumption
$C_{aorta}O_2$: oxygen content in arterial blood
$C_{mixed\ venous}O_2$: oxygen content of mixed venous blood

Oxygen content is calculated from the following formula:

$$O_2\ Content = \left(1.34 \times Hb \times \frac{\%Saturation}{100}\right) + 0.003 \times PaO_2$$

where
Hb: haemoglobin (g/l)
PaO_2: partial pressure of oxygen in arterial blood (mmHg)

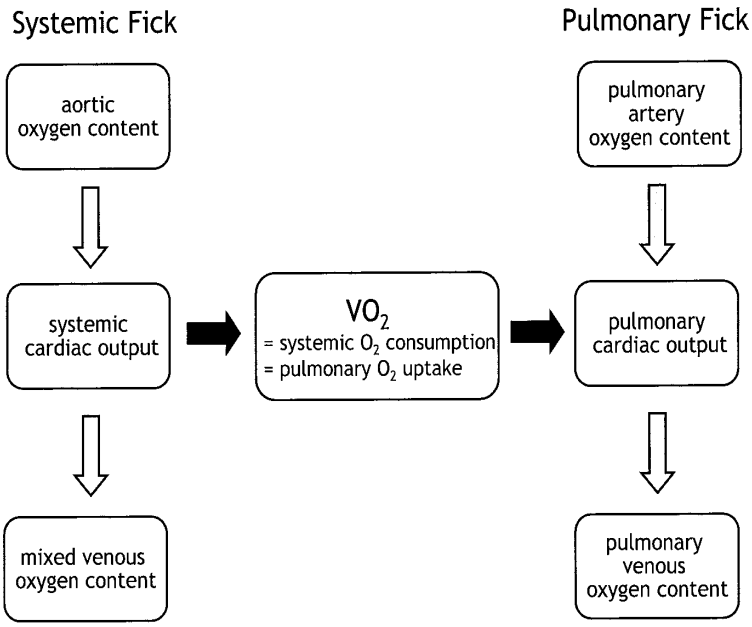

Figure 1-1 Fick principle. Cardiac output is calculated from estimation of oxygen consumption (pulmonary uptake) and difference between the oxygen content at an upstream and downstream point. Reproduced from: Halley G, Tibby S. Haemodynamic monitoring . In: Roger's Text book of Paediatric Intensive Care, Lippincott Williams & Wilkins 2008.[18]

Direct measurement of these variables constitutes the direct Fick method. The Fick method can be used to calculate both systemic cardiac output and pulmonary blood flow. Normally, pulmonary blood flow is equal to systemic cardiac output. However, in diseased states or in conditions with anatomic shunts, this equilibrium may not necessarily hold true and requires careful consideration of which flow is being measured and the upstream and downstream sampling sites (fig 1-2).

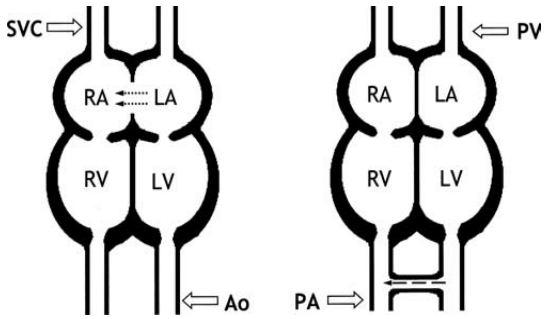

Figure 1-2 Calculation of pulmonary and systemic blood flow in the presence of anatomic shunts. Diagram on the left has ASD (left to right shunting). For systemic cardiac output, mixed venous estimation should be done upstream from the shunt such as from SVC . The right diagram shows a patent ductus arteriosus, again with left to right flow. The mixed venous estimation should be done from the pulmonary artery 'downstream' to the shunt to allow estimation of total pulmonary blood flow. Ao = aorta; LA = left atrium; PA = pulmonary artery; PV = pulmonary veins;; RA = right atrium; RV =right ventricle; LV = left ventricle; SVC = superior vena cava. Reproduced from: Halley G, Tibby S. Haemodynamic monitoring . In: Roger's Text book of Paediatric Intensive Care, Lippincott Williams & Wilkins 2008.[18].

Fick is an accurate method for CO estimation but it has several technical challenges and sources of errors in addition to being time consuming and labour intense.[19]

Technical challenges

Firstly, the Fick technique requires measurement of oxygen consumption or carbon dioxide production. Traditional methods such as Douglas bag and spirometry are impractical to use in PICU settings. Modern, portable metabolic monitors or mass spectroscopy has replaced these.

Secondly, oxygen content measurement (see formula above) requires arterial and pulmonary artery catheters for arterial and mixed venous blood sampling.

Sources of error for Fick method

The Fick method is prone to numerous sources of error; both in estimating oxygen consumption and arterial and mixed venous oxygen content calculation.

Errors in estimating oxygen consumption

(i) Loss of expired gas: Leaks around the endotracheal tubes and pneumothorax with associated bronchopleural fistula allow expired air to escape the metabolic monitors resulting in inaccurate estimations. A cuffed endotracheal tube is recommended to minimise the errors due to leaks.[20]

(ii) High fractional inspiratory oxygen: Most modern metabolic monitors employ the Haldane algorithm to estimate oxygen consumption.[21] The difference between the inspiratory and expiratory oxygen concentration is small with high fractional inspiratory oxygen concentration requirements for example in conditions with severe lung disease. This leads to an error in the denominator part of the Haldane algorithm. .This error is more pronounced with FiO_2 greater than 0.85.[22]

(iii) Severe lung pathology may violate the law of mass balance (systemic oxygen consumption is in equilibrium with oxygen uptake by the lungs). Oxygen consumption of normal lungs is accounted for in the Fick equation. However, in severe pulmonary disease, lungs may consume oxygen directly from the inspired oxygen, rather than via the bronchial circulation. This leads to a difference in measured oxygen uptake (greater) and systemic oxygen consumption resulting in overestimation of cardiac output.[23]

(iv) Estimation of mixed venous saturations is sometimes performed using central venous rather than pulmonary arterial blood. This assumes a constant and small difference between the two sites, which is not guaranteed in critically ill patients. The range of limits of agreement between the two is reported as ±15 to ± 25%. This error is variable rather than fixed and is influenced by multiple factors such as venous sampling site, shunts, redistribution of blood flow, depth of anaesthesia and myocardial oxygen consumption.[24]

(v) Other steps prone to errors in this technique are the conversion of gas volumes to standard conditions and controlling partial pressure of water vapours to desired effect.

(ii) Partial carbondi-oxide (CO_2) rebreathing or Indirect Fick method

An alternative to direct invasive vascular access is to estimate the Fick parameters indirectly from the inspired and expired gases using a partial CO_2 rebreathing technique. This is known as indirect Fick method. It involves introduction of a fixed volume of dead space into the ventilator circuit. The patient rebreathes a proportion of the exhaled CO_2 for a short duration while mechanically ventilated. Parameters are measured before and after the CO_2 rebreathing period once equilibrium is established and pulmonary capillary blood flow is calculated as follows:

$$Qpcbf = \frac{\Delta VCO_2}{\Delta C mixed\ venous - \Delta C pulmonary\ end\ capillary}$$

where

Qpcbf: pulmonary capillary blood flow

ΔVCO_2: measurement of change in CO_2 production before and after rebreathe

ΔC mixed venous: change in CO_2 content in mixed venous blood before and after rebreathe and is assumed to be zero

ΔC pulmonary end capillary: change in CO_2 content in pulmonary end capillaries before and after rebreathing. This is estimated from alveolar CO_2 content which in turn is estimated from end tidal CO_2 via a correction factor

Nunn's iso-shunt diagrams are used to estimate intrapulmonary shunt flow and added to pulmonary capillary blood flow to give total pulmonary blood flow.[25]

Sources of error for Indirect Fick method

(i) Indirect Fick method assumes no restriction of diffusion of CO_2 across the alveolar membrane. This may not be entirely true in patients with severe lung injury who have deranged alveolar gas exchange thus affecting the CO calculation.[26]

(ii) The effects of unknown ventilation perfusion mismatch or shunts may result in underestimation of cardiac output.[27] Measurement of arterial $PaCO_2$ is necessary when the dead space is large ($\frac{\text{Dead space volume}}{\text{Tidal volume}}$ > 0.65) in conditions such as pneumonia or acute respiratory distress syndrome; as estimation of $PaCO_2$ from the end tidal CO_2 will be inaccurate. This is more likely to be the case in clinical practise in PICU settings.[28,29]

(iii) The relationship between $PaCO_2$ and end tidal CO_2 is only true for the linear part of the CO_2 dissociation curve ($PaCO_2$ greater than 30 mm of Hg). Hyperventilation leading to a $PaCO_2$ less than this value will make this an invalid assumption.[30]

Summary of paediatric studies using Fick and Indirect Fick method

Only a limited number of studies have evaluated these methods in a paediatric population. Table 1-1 below illustrates the summary of some of the studies using direct and indirect Fick method. These studies suggest that direct Fick method is in good agreement with pulmonary artery thermodilution method (PATD). However, indirect Fick lacked agreement when compared with PATD.

Table 1-1 Representative summary of paediatric studies using Direct and Indirect Fick technique

Author (year)	Technique	Ref.	N	Weight (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Wippermann[31] (1996)	Fick-O_2	PATD	25	na+	na+	-0.05	0.32	21.3	na+
Levy [32] (2004)	CO_2 R	PATD	37	9.2 – 47.4	1.2-5.4	-0.27	1.49	53*	0.83
Botte [33] (2006)	CO_2 R	TTE	21	15 – 60	1.8-9.9	-0.61	0.94	20	0.85

CO_2R = Carbon dioxide rebreathe; LOA = limits of agreement; N = number of subjects; na^+ = Not available; PATD = pulmonary artery thermodilution; PE = Percentage error; R = Reference method; TTE = trans thoracic echocardiography; Weight and CO are expressed as range.* Value not provided but estimated from the data provided.

1.2.2 Indicator dilution methods

Stewart, first used the indicator dilution method for measurement of blood volume flow in 1827 .[34] Hamilton subsequently utilised this principle to measure cardiac output.[35]

A variety of dilution methods are available; all are based on the same principle, regardless of the indicator used (temperature, dye, charge, ultrasound velocity). Injecting a known amount of indicator into the venous blood stream and measuring the temporal change in blood-indicator concentration downstream allows for generation of a dilution curve, from which blood flow may be calculated. The dilution curve rises to a peak level and decays exponentially with the curve never returning to the baseline. This mono-exponential decay is a result of the ventricle ejecting only a fraction of its content with each systole, leaving a part of the indicator within the ventricle. Indicator free venous blood returning to the heart dilutes the indicator during diastole and again only a fraction of this is ejected out of the ventricle. This cycle continues until recirculation of the indicator happens. Extrapolating the decay curve from just before the point of recirculation enables calculation of the area under the curve. This is achieved by semi-logarithmic conversion, which converts the decay curve into a straight line that is extrapolated to the baseline. The characteristics and shape of the curve depend upon the site of measurement of the indicator concentration (pulmonary artery or transpulmonary dilution methods) (fig 1-3).

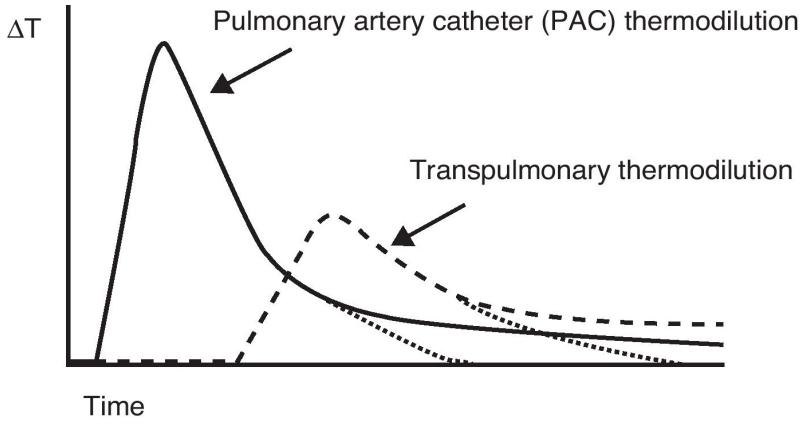

Figure 1-3 Comparison of thermodilution curves generated with thermistor in the pulmonary artery and further downstream (transpulmonary). The transpulmonary thermodilution curve has a delayed appearance and a smaller peak. However, both the curves approximate a similar baseline. Adapted from: Reuter et al, Anesth Analg 2010;110:799 –811 [36].

Indicator dilution methods use Stewart–Hamilton equation (see below) for calculation of cardiac output:

$$CO = \frac{Amount\ of\ indicator\ injected}{\int_0^{\infty} Concentration\ of\ indicator(t)\,dt}$$

where

the denominator refers to the integral of the indicator concentration with time. This is represented by area under the curve (AUC) for indicator concentration versus time measured between time of injection and infinity. Hence, there is an inverse relationship between CO and AUC. High flow situations produce narrow peaked curves where as low flow situations produce broad and large dilutional curves.

Sources of error for Indicator dilution methods

Indicator dilution methods are accurate as long as there is a rapid and even indicator injection, complete mixing of the indicator and blood, no loss of indicator between injection and measurement, no anatomical shunt, minimal valve regurgitation, and steady state flow. Any deviation from these characteristics as explained below, will impact on the accuracy of the measurements.

(i) Loss of indicator before injection [37] (in terms of both the volume or temperature of the injectate) , during the injection due to catheter dead space and conductive warming (the latter only in cases of thermal indicator) [38] or after the injection as a result of conductive rewarming (with thermal indicator) [39] can lead to reduction in the mean blood temperature fall. This leads to a reduction in area under the curve, hence, overestimation of cardiac output by a considerable measure.

(ii) Pathological recirculation of the indicator in situations of anatomical shunts or low cardiac output state increases the AUC hence underestimates the cardiac output. The shunt allows the indicator to recirculate and get detected multiple times.[40]

(iii) Tricuspid regurgitation leads to inaccurate estimation in either direction. Reverse movement of the indicator during ventricular contraction is one of the contributory factors.[41]

(iv) Fluctuations in the baseline temperature due to changing clinical conditions like rewarming [42], after cardiopulmonary bypass [43] and cyclical changes in CO during different phases of respiration may also lead to inaccuracies in CO estimation.

Types of Indicator dilution methods

(i) Thermodilution methods

The thermodilution method utilises cold saline as an indicator and measures changes in the blood temperature downstream. The Stewart–Hamilton equation can be rewritten as:

$$CO = \frac{V_0(T_b - T_0)K}{\int \Delta T_b \, dt}$$

where

V_0 and T_0: volume and temperature of the injectate respectively

Tb: temperature of the whole blood prior to injectate

$\int \Delta Tb \, dt$: time averaged temperature change

K: heat constant [36]

Cardiac output will be inversely proportional to the mean blood temperature depression and the duration of the transit of the cooled blood.

Thermodilution techniques are further subdivided into pulmonary artery thermodilution and transpulmonary thermodilution.

Pulmonary artery thermodilution (PATD)

a) Intermittent pulmonary artery thermodilution

This method involves an indicator of known volume and temperature injected via the proximal port of pulmonary artery catheter (PAC) into the right atrium. The original description was with the use of cold saline or dextrose.[44] The indicator mixes with the blood, travels to the right ventricle and further into the pulmonary artery. The change in the blood temperature is detected by the thermistor at the catheter tip within the pulmonary artery, and produces a thermodilution curve enabling CO measurement. The technique has been validated with various other standardized techniques, such as Fick principle[45] or electromagnetic flow probes.[46] The accuracy of this method is reasonable, provided readings are performed meticulously. The quoted precision error of triplicate readings of approximately 13% made this a clinical reference standard for a many years.[47]

Although this method is often regarded as a benchmark method in clinical practice, it is not a gold standard and has technical challenges and other potential sources of inaccuracy in addition to the generic errors described previously. These include technical complications for placement of PAC such as tissue damage, arrhythmias, catheter malposition, haemothorax, pulmonary infarction, sepsis.[48] In addition, variations in blood temperature within the pulmonary artery that is unrelated to indicator injection and fluctuations in cardiac output as a result of positive pressure ventilation mandates averaging of multiple measurements timed throughout the ventilator cycle.[49,50]

b) Continuous pulmonary artery thermodilution

This method has the same principles as the bolus pulmonary artery thermodilution. However, instead of injecting cold saline intermittently, there is a heating filament attached to the PAC 15-25 cm before its tip. Depending upon the make of the monitor, either a flat heating filament is activated for 1-4 s using a pseudorandom binary sequence to produce constant heat or a coiled filament emits heat for 20 seconds of a 40-seconds repetitive on-off cycle. This signal in either case is picked up by the thermistor at the end of the catheter producing a thermodilution curve after averaging.[51,52]

Continuous pulmonary artery thermodilution has been shown to have good correlation with the intermittent bolus method in different clinical conditions.[53,54] The main disadvantage of this method is the time lag of up to 5 minutes for averaging during period of haemodynamic instability.[55] This could be classed as a continuous but not instantaneous system. Another disadvantage is its reported inaccuracy in patients recovering from hypothermia possibly due to generation of small heat signals as compared to the large cold signal with intermittent bolus technique.[56]

Transpulmonary thermodilution (TPTD)

This method is similar to pulmonary artery thermodilution but the temperature change is measured typically in a large systemic artery such as the femoral artery. This obviates the need for introduction of PAC. One of the advantages of TPTD over pulmonary artery thermodilution is it's less susceptibility to changes in CO induced by mechanical ventilation. It is due to a relatively long time interval between injection and sensing site (as compared to PATD) during which 3-4 cardiac cycles occur. This averages out any cyclical SV changes related to mechanical ventilation. The thermal indicator is injected into the superior venacava, mixes with the surrounding blood, traverses through the right side of the heart, pulmonary circulation, left side of the heart and aorta and is detected at a downstream location (for example a major branch of femoral artery).[57] This produces a thermodilution curve similar to intermittent bolus

pulmonary artery thermodilution method from which CO is calculated using Stewart–Hamilton equation. Figure 1-3 compares pulmonary and transpulmonary thermodilution curves after injection of cold injectate into the superior venacava. The PATD curve has a higher peak and arrives early after the injection with the thermistor in the PA as compared to TPTD, where temperature detection is further downstream in the aorta. However, both curves approximate similar baselines.

Initially there were concerns regarding the loss of indicator between injection and measurement. In fact several authors have demonstrated that the loss of heat is small and relatively constant without affecting the accuracy of cardiac output measurement provided the injectate is cooled sufficiently (to less than 10 degree C).[58,59] In addition this small loss of heat has been utilized to calculate extravascular lung water, which may be used as a marker of disease severity in certain states (e.g. acute respiratory distress syndrome).[60,61]

TPTD does not involve PAC insertion thus avoids many of the associated risks . This makes it more attractive for use in small paediatric patients. In addition to measuring CO, this technique also provides variables such as intra-thoracic blood volume and global end diastolic volume – markers for estimation of preload based upon the concept of mean transit time and exponential downslope time of the primary thermodilution curve (see chapter 2).[62-64]

One obvious disadvantage over intermittent bolus pulmonary artery thermodilution is its inability to provide or estimate PA pressures or true mixed venous saturations. TPTD is amenable to the same sources of error as intermittent bolus pulmonary artery thermodilution as they both use the same principles but is less prone to ventilator induced fluctuations in CO.

TPTD has been compared with pulmonary artery thermodilution [65] and Fick method [66] in both paediatric and adult patient population.[67] The majority of studies report an acceptable level of error between the two (see table 1-2).

(ii) Transpulmonary ultrasound dilution method (CO Status™, Transonic, NY, USA)

The transpulmonary ultrasound dilution technique (TPUD) is based upon the principles of indicator dilution method with normal saline as an indicator. It utilises an ultrasound beam passing through an extra-corporeal arterio-venous (AV) loop attached to a central venous and arterial catheter. A roller pump provides a constant blood flow rate 9-12 ml/min in the AV loop. Normal saline (0.5–1 ml/kg, maximum 30ml) at body temperature is used as an indicator, and injected via the venous limb. The velocity of the ultrasound beam directed through a column of isotonic saline at body temperature is 1533 m/sec, which is different from that of blood (ranging typically between 1570 – 1585 m/sec). Thus, saline injected into the venous limb will produce a transient change in ultrasound velocity in both the venous and arterial limbs, in proportion to the degree of dilution. This is expressed graphically on the monitor as an arterial dilution curve. The arterial dilution curve can be used to calculate cardiac output via the Stewart-Hamilton equation. A more detailed description of the technique is provided in chapter 3. The theory and in-vitro validation of this technique is reported in detail by Krivitsky et al.[68]

(iii) Transpulmonary Lithium dilution method (TPLD)

TPLD is an indicator dilution technique based upon the same principles as TPTD. However, instead of the cold saline, Lithium chloride (LiCl) is used as an indicator injection through a peripheral or central vein. LiCl mixes with the venous blood, traverses through the right ventricle and lungs and is ejected in the arterial system by the left ventricle. Sampling arterial blood through a Li ion selective electrode or a sensor situated in a flow through cell with the help of a mechanical pump generates the concentration time curve (fig 1-4).

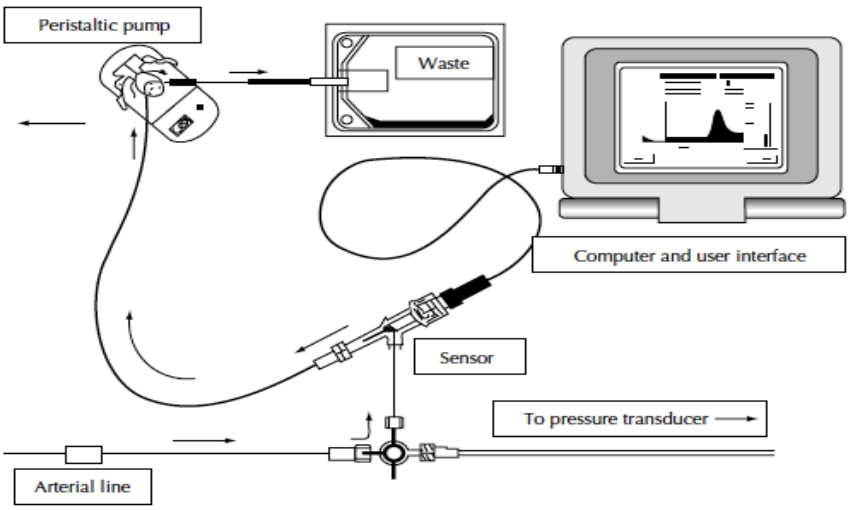

Figure 1-4 Set up for Transpulmonary Lithium dilution method. Arterial blood passes through a Lithium ion selective electrode (in earlier versions of the technology) or a sensor situated in a flow through cell generating a concentration time curve. Reproduced from: Jonas M and Tanser S. Curr Opinion in Crit Care 2002;8:257-261.[69]

The electrode contains membrane selectively permeable to lithium. The change in voltage across the membrane is related to the change in plasma Lithium concentration with plasma sodium concentration correction using the Nernst equation.

$$CO = \frac{LiCl \times 60}{Area\ (1 - PCV)}$$

where
LiCl: dose of LiCl injected
Area: area under the lithium dilution curve and
PCV: packed cell volume

The technique does not require a PAC but is vulnerable to the same sources of error as the thermodilution method (discussed above).

Limitations of Lithium Chloride method

LiCl method has some unique limitations in addition to the generalised limitations associated with indicator dilution methods.

(i) It can not be used on patients on Li therapy, as the increased background Lithium concentration will interfere with the CO estimation (overestimation).

(ii) Non-depolarising muscle relaxants (Pancuronium, Vecuronium) may cause a drift in the electrode leading to inaccurate results.[70]

(iii) Blood sampling is required for every measurement (as in other indicator dilution techniques) which may lead to iatrogenic anaemia in small paediatric patients.

(iv) Lastly, rapid repeated measurements are hindered by the persistence of Li in the blood for a short duration of time.

TPLD has been validated against TPTD [71], electro-flowmetry [72] with good correlation in human and animal models respectively (see table 1-2). Linton et al, in their study involving twenty eight children between the age 5 days to 9 years , compared TPLD with TPTD. They reported near acceptable percentage error of 32% for agreement between the two methods. The authors did not report any complications hence, suggesting it to be safe and accurate in the paediatric population.[73]

iv) Dye dilution technique

Indocyanine green (ICG) was the most commonly used dye in this method (however, it is not available commercially now). ICG is injected via a central vein and change in concentration over time is measured in a systemic artery utilising photometric technique.

Limitations of Dye dilution method

There are three main limitations of its use.

(i) Firstly, a densitometer requiring calibration with a sample of patient's blood with known dye concentration is used for concentration–time curve. This is a labour intense and time consuming process.

(ii) Secondly, each measurement requires blood sampling. Use of fibre optic sensors in pulse dye densitometry has overcome the first two limitations. Here, the arterial concentration is measured noninvasively by a finger tip light emitting sensor (wavelength 805 and 890 nm). The ratio of ICG concentration measured at these wavelengths is used to derive the ICG concentration time curve.[74]

(iii) Thirdly, ICG is metabolised by liver, hence recirculation restricts the time between successive measurements, which is further exacerbated in significant liver failure patients.
Various studies have compared this technique with other methods with conflicting results.[75-77] Hence, this method has not gained widespread popularity in clinical use.

Summary of paediatric studies using indicator dilution methods

Table 1-2 below presents some of the studies using different indicator dilution methods in paediatric settings. Among these, TPTD has shown very good agreement with the direct Fick and pulmonary artery thermodilution method. Percentage error between TPLD and TPTD was just above the acceptable value of 30% to demonstrate agreement between the two. TPUD also showed agreement with pulmonary artery thermodilution and very nearly with ultrasound flow probes with an error of 31%.

Table 1-2 Representative summary of paediatric studies using indicator dilution techniques

Author (year)	Technique	Ref.	N	Weight (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Pauli [58] (2002)	TPTD	O_2 Fick	18	4.3 – 88	0.4 – 6.2	0.06	0.38	10.7	0.99
Tibby [66] (1997)	TPTD	O_2 Fick	24	2.5 – 60	0.24 – 8.7	0.03	0.49	19	0.99
Mcluckie [65] (1996)	TPTD	PATD	9	9.8 – 23.7	3 – 5.3	0.19	0.42	9.5	na
Linton [73] (2000)	TPLD	TPTD	17	2.6 – 34	0.4 – 6	-0.10	0.62	31.8	0.96
* Crittendon [78] (2012)	TPUD	PATD	28	9.4 – 73.8	1.85 - 4.49	-0.004	0.8	25.4	0.95
*Lindberg [79] (2014)	TPUD	UFP	21	3.2 – 11.8	0.52 - 1.54	-0.02	0.3	31	na

LOA = limits of agreement; N = number of subjects; na = Not available; PATD = pulmonary artery thermodilution; PE = Percentage error; Ref. = Reference method; TPTD = Transpulmonary thermodilution; TPUD = Transpulmonary ultrasound dilution; UFP = Ultrasound flow probe; Weight and CO are expressed as range. * =Studies published after commencement of MD.

1.2.3 Ultrasound Techniques

(i) Transoesophageal Doppler ultrasound (TOD)

Franklin first applied the Doppler principle for measurement of blood flow in 1961.[80]

The theory of Doppler states that the shift in the frequency of the reflected ultrasound wave is proportional to the velocity of the moving object (red blood cells).[81]

$$V = \frac{\Delta f \times c}{2 f_t \times \cos\theta}$$

where

V: velocity of the blood (measured)

Δ f : frequency shift between transmitted and reflected signal

c: Ultrasound velocity in blood (1540m/s)

θ: angle of incidence referred as the angle formed between the ultrasound beam and the target direction of flow and is assumed to be 45 degrees and

ft = transmitting frequency

Doppler ultrasound can be applied continuous or pulsed. It can be applied to any pulsatile vessel. However, CO measurement is typically performed in the aorta via transthoracic or trans-oesophageal route. The latter has the potential to be used for continuous measurements.[82] The velocity-time signal characteristically shows a triangular shape. This also allows derivation of several flow-related variables (fig 1-5).

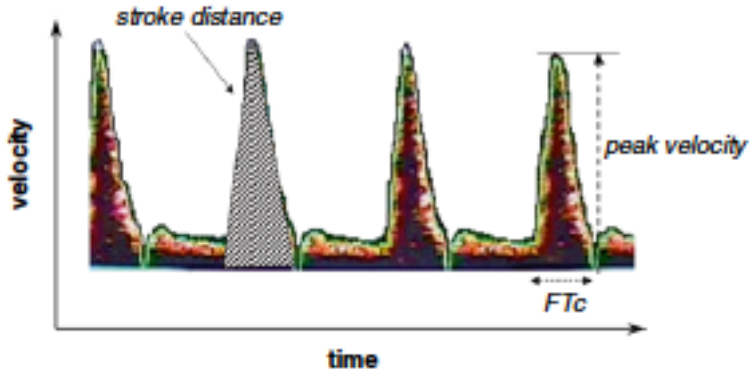

Figure 1-5 Velocity time spectral representation from measurements involving aorta. The hatched area under the triangle represents stroke distance. Reproduced from: Tibby S. Haemodynamic monitoring.In: Paediatric Critical Care Medicine.London:Springer;2014. [3]

The integral of velocity-time (area under the triangle) represents stroke distance. It is the distance that a column of blood will travel along the aorta in one cardiac cycle.

Conversion of stroke distance to stroke volume requires multiplication by the cross-sectional area of the vessel through which flow is occurring.

$$SV = VTI \times \frac{\pi D^2}{4}$$

where
SV: stroke volume
VTI: velocity- time integral calculated using Doppler ultrasound or stroke distance
D: diameter of the vessel through which flow is occurring

'D' can either be measured directly using echocardiography [83], or calculated using nomograms based upon age, sex, weight and height [84]. Echocardiography (either M mode or 2-dimensional) can be used at a variety of sites such as aortic valve annulus or root, ascending or descending aorta. Out of these, the measurement of the left ventricular outflow diameter at the valvular annulus using 2-D echocardiography during systole is considered most accurate.[85,86]

Another variable is Corrected Flow Time (FTc). This is defined as the time from the beginning of the aortic pulse upstroke to its return to the baseline. This will be affected by the native heart rate, hence is corrected for a baseline heart rate of 60 beats per minute using Bazett's equation:

$$FTc = \frac{FT}{\sqrt{RR}}$$

where
FT_C: corrected flow time
FT: flow time
RR: interval between two consecutive R waves on ECG

Several studies have compared this with other established markers of cardiac preload with good agreement.[87,88]

Several oesophageal Doppler probes are available commercially: ODM II™(Abbott, Maidenhead, UK), CardioQ™(Deltex Medical Ltd, Chichester, Sussex, UK), and HemoSonic100™(Arrow, Reading, PA, USA).

Sources of error for Doppler methods

(i) Range ambiguity and aliasing: Continuous-wave Doppler employed in most stand-alone Doppler techniques consider all blood flow within the path of the beam (i.e., not only flow across the aortic valve), resulting in range ambiguity. Range ambiguity is defined as the inability of the imaging system to precisely localize the source (location) of the reflected signal in the heart. A Pulsed-wave (PW) Doppler ultrasonography has an advantage over continuous wave (CW) Doppler in that by measurement of the time interval between the "send" and "receive" signals the location of the source of the ultrasound signal can be accurately measured. This permits "gating" of the signal to a particular region of interest. The disadvantage of PW Doppler is that the maximal velocity of blood flow which can be measured is not as high as CW Doppler. In order to achieve the highest possible ability to measure high flow, a low frequency transducer is necessary with a region of interest close to the transducer. If the maximum velocity (Nyquist limit) is exceeded the Doppler signal will "alias" making it impossible to measure maximal flow velocity and its direction.[88]

(ii) Flow measured in descending aorta excludes blood flow to the arch and its vessels. A correction factor of approximately 30% is applied for the blood flow in the cephalic aorta in nomograms for adult patients. However, this proportion is not fixed and may alter in different haemodynamic states. This correction factor is not included in paediatric nomogram. Tibby et al derived a nomogram using transoesophageal Doppler for estimating CO from patient height and mean distance (analogous to mean velocity per minute, which is practically same in ascending, transverse and descending aorta). Hence, no correction factor is required for the estimation of CO.[89]

(iii) Cross sectional area of aorta is not fixed and varies depending upon the vascular tone, volume status and inotropy. Hence, this introduces errors especially when the area is estimated from nomograms rather than direct measurements.[90]

(iv) Position of the probe is important and a crucial step in the estimation of CO making it vulnerable to operator dependent errors. The angle of insonation between the Doppler beam and direction of blood flow should be less than 15° (unless angle correction is applied) in order to get the best approximations.[91,92]

(v) The flow in the aorta may not always be laminar. Conditions such as anaemia, tachycardia and aortic valve disease will result in turbulent flow thus altering the velocity measurements leading to further errors.[91]

Summary of paediatric studies using oesophageal Doppler methods

Several authors have compared this technique with various other methods both in paediatric and adult patients. Chew et al, reviewed systematically the accuracy and repeatability of Doppler use in paediatric cardiac output estimation. They included studies comparing Doppler flow measurements with thermodilution, Fick or dye dilution methods in paediatric critical care settings. They demonstrated a pooled precision of 30%, bias generally less than 10% and repeatability between 1-22%. They made an important recommendation that Doppler CO

measurement is acceptably reproducible in paediatric population especially when used for tracking changes rather than the absolute values.[93]

Table 1-3 summarises some of the comparison studies of oesophageal Doppler with other reference methods in paediatric patients. Tibby et al did not report percentage error as the study was designed for creation of a paediatric nomogram for estimation of CO using minute distance and patient height. The two other authors (Schubert and Knirsch) reported a high percentage error hence, poor agreement between oesophageal Doppler and transthoracic echocardiography or PATD. Both the authors did not investigate the tracking ability of changes in CO of oesophageal Doppler following interventions aimed to augment CO.

Table 1-3 Summary of representative paediatric studies with transoesophageal Doppler

Author (year)	Technique	Ref.	N	Weight (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Tibby [94] (2000)	OD	TPTD	100	3 - 70	0.32 - 9.19	na[+]	na[+]	na[+]	0.82
Schubert [95] (2008)	OD	TTE	26	2.6 – 47	0.9 – 3.7	0.36	1.67	71[*]	0.72
Knirsch [96] (2008)	OD	PATD	40	3.4 – 59.4	1.2 -7.1	0.66	1.79	54.3	0.65

OD = Transoesophageal Doppler; LOA = limits of agreement; N = number of subjects; na[+] = Not available as the study objective was derivation of the normogram; PATD = pulmonary artery thermodilution; PE = Percentage error; Ref. = Reference method; TPTD = Transpulmonary thermodilution; TTE = Transthoracic echocardiography; Weight and CO are expressed as range; [*] = calculated from the data /graph provided.

Transcutaneous Doppler ultrasound (USCOM ™)

This non invasive, continuous wave Doppler based technique involves probe placement in the suprasternal notch or parasternal region, targeting the aortic or pulmonary valve respectively (USCOM™, Sydney, Australia). It utilises nomograms for the estimation of cross sectional area at the aortic and pulmonary valves. One of the advantages is the measurement of CO in the ascending aorta . Thus, no assumptions are made regarding the percentage of flow of total CO making its way to the descending aorta.

However, transcutaneous Doppler has higher inter- and intra- user variability, as compared to transoesophageal Doppler.[93]

Summary of paediatric studies using transcutaneous Doppler (USCOM ™)

Several authors have evaluated transcutaneous Doppler in paediatric setting. Knirsch et al compared this method with pulmonary artery thermodilution . They demonstrated a percentage error of 36% and did not reliably measure absolute CO values. However, Phillips et al compared this against echo Doppler in 37 preterm neonates and showed good correlation between the two. A representative summary is tabulated below in table 1-4. Transcutaneous Doppler did not show good agreement with any of the reference methods in the paediatric age group. In addition, Mohan et al reported a large coefficient of variation of approximately 16% implying poor repeatability.

Table 1-4 Summary of representative paediatric studies with transcutaneous Doppler (USCOM)

Author (year)	Technique	Ref.	N	Weight (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Knirsch [97] (2008)	TCD	PATD	24	3.4 - 51	1.3 - 5.3	-0.13	1.34	36	na+
Mohan [98] (2002)	TCD	TOD	20	5 – 60	na	27.6% change	na+	na+	na+
Phillips [99] (2006)	TCD	TTE	37	0.66 - 1.6	na	0	0.16	46*	0.91

LOA = limits of agreement; N = number of subjects; na+ = Not available in the manuscript; PATD = pulmonary artery thermodilution; PE = Percentage error; Ref. = Reference method; TCD = Transcutaneous Doppler; TOD = Transoesophageal Doppler; TTE = Transthoracic echocardiography; Weight and CO are expressed as range; * approximate calculation from Bland Altman graph and data provided in the manuscript.

(iii) Transthoracic echocardiography

Transthoracic echocardiography can be used in two ways for the estimation of stroke volume or CO. The first method involves volumetric measurements for estimating the volume of the left ventricle at the end of the diastole and systole. The difference between the two is the stroke volume.

The second method involves a pulsed Doppler aortic blood flow estimation at the exact level of the aortic annulus from the apical five-chamber view (see fig 2-10 on page 123). The aortic velocity–time integral (VTIao) is derived as a mean of three to five consecutive measurements over a single respiratory cycle. LV stroke volume (ml) and cardiac output (l/min) are determined using the following formula:

$$SV = VTIao \times \frac{\pi D^2}{4}$$

where
SV: stroke volume

VTIao: velocity time integral at the aortic annulus
D: diameter of the aortic annulus either estimated from nomogram or measured using echocardiography

Recently, contrast echocardiography has shown promising results in the measurement of CO [100].

However, echocardiographic estimation of CO is not continuous and requires a skilled operator which may not be readily available. In addition, accurate estimation of LV volumes is challenging by routinely available 2D echocardiography even by most experienced operator. [101,102] Hence this method has not gained widespread popularity especially in paediatric intensive care settings.

1.2.4 Arterial pulse contour analysis

The arterial pulse contour method estimates stroke volume (hence CO) from the analysis of arterial pulse pressure waveform on a beat-to-beat basis. This technique requires an arterial catheter, which is commonly placed in the majority of critically ill patients as part of routine haemodynamic monitoring. This continuous monitoring system allows rapid tracking of haemodynamic changes.

Otto Frank in 1899, first introduced the concept of measuring blood flow changes using blood pressure waveforms. He described the circulation with his Windkessel (air chamber) model which forms the basis of many of the modern pulse contour analysis methods.[103]

The Windkessel model represented the heart and the systemic arterial system with a closed hydraulic water filled circuit along with a water pump connected to a chamber partially filled with air.[104] The water was pumped into the chamber by the pump (representing the heart) thus compressing the air in the chamber. This pushed water back out of the chamber into the circuit towards the pump. The compressibility of the air in the pocket represented the elasticity and extensibility of the major arterial system as the heart pumps blood into them. This was referred to as arterial compliance. The resistance encountered by the water in leaving the Windkessel equates to the resistance faced by the blood while flowing through the arterial system. This comprised peripheral resistance. This simplistic '2 element Windkessel model' helped in calculating flow using Ohm's law (fig 1-6).

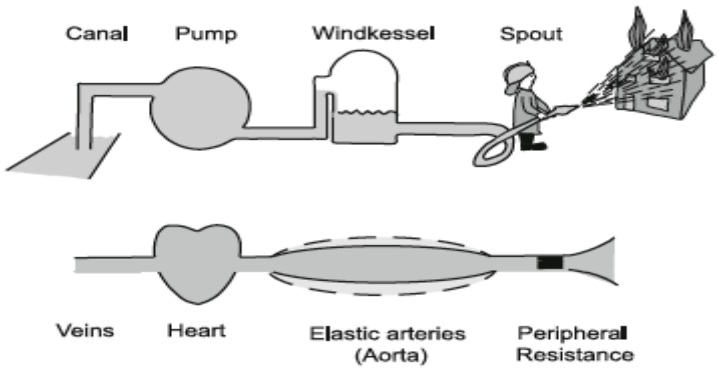

Figure 1-6 The concept of the 2-element Windkessel model, comprising compliance/elastance and peripheral resistance. The large arteries act as the Windkessel (air chamber) as a result of their vascular properties. Reproduced from: Westerhof N,et al.J. Biomech. 1969:2, 121-143.[105]

The model was further improved to a 3 and 4 element Windkessel model introducing impedance [106] and arterial inertance [107] respectively. This improved the accuracy of algorithm for stroke volume estimation from the arterial pulse pressure curve. This algorithm was initially described by Wesseling et al [108] based upon the assumption that stroke volume is directly proportional to the area under the systolic portion of the arterial pressure waveform.

Sources of error for pulse contour methods

(i) These methods rely on the characteristics of arterial pressure waveform; hence, any factors that affect these characteristics may introduce inaccuracies in the CO estimation. This includes age, disease or inotrope related changes in the vessel wall characteristics. Arrhythmias change the characteristics of arterial waveform hence, are important and common sources of error leading to inaccurate results.

(ii) The contour of the arterial pressure waveform changes significantly throughout the forward motion of the arterial pulse.[109] Thus, insertion of arterial catheter at different places may affect the waveform leading to interference with CO estimation (fig1-7).[110]

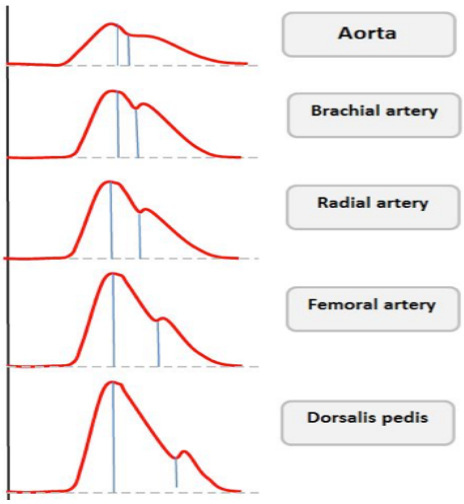

Figure 1-7 Contour of arterial pressure waveform at different sites. The peak systolic and diastolic pressure readings vary according to the position of the catheter. However, the mean blood pressure is the same, as it is estimated from area under the curve, which remains same irrespective of the catheter position.

(iii) Changes in the calibre of the vessels and bifurcations can lead to reflection of the pulse pressure wave creating further interference.[111]

(iv)The pressure transducers routinely used in clinical practice may be under or over damped contributing to imperfect waveforms and inaccurate measurements.[112]

(v) The aortic valve incompetence will compromise the accuracy of these methods due to diastolic run off.

(vi) Changes in arterial load parameters especially arterial compliance and elastance as a result of either pathology or treatment (volume expansion or vasoactive therapy) can lead to inaccurate estimation of cardiac output.[113]

Different types of pulse contour methods

Currently arterial pulse contour analysis methods are broadly divided into methods requiring calibration or uncalibrated methods as described below.

(i) Calibrated methods

a) Pulse contour cardiac output (PiCCO, Pulsion, Munich, Germany)

This method determines stroke volume from the systolic portion of the arterial pressure waveform. It requires manual calibration to incorporate inter and intra individual changes in resistance and compliance as a result of changing clinical conditions.[114]

The arterial pulse contour method is calibrated using an average of three to five transpulmonary thermodilution measurements of cardiac output. The recalibration interval depends upon the haemodynamic stability of the patient, with shorter recalibration intervals recommended in unstable patients.[115,116]

Fakler et al in a paediatric cohort demonstrated a strong correlation between transpulmonary thermodilution and contour analysis cardiac indices (Pearson correlation coefficient r = 0.93; coefficient of determination r2 = 0.86). The mean bias between cardiac indices derived by thermodilution and those derived by pulse contour analysis over all data points was 0.05 (SD 0.4) L /min /m^2 (95% conf. intv. 0.01-0.10).[117]

b) Pulse power analysis (LiDCO^{TM} plus, UK)

Pulse power analysis method counteracts some of the limitations mentioned above. It is based upon the law of conservation of mass and an assumption that pulse power is proportional to the stroke volume. The arterial pressure signal is corrected to a standardized waveform which derives net effective beat power factor after auto-correlation proportional to the nominal stroke volume. The nominal stroke volume is converted to actual stroke volume by an independent

indicator dilution measurement using Lithium chloride (explained earlier) taking into account the arterial tree compliance. Lithium chloride injection can be done by a peripheral cannula and measurements for construction of dilution curve can be obtained by a sensor connected to radial artery. Pulse power algorithm is less prone to errors due to damping, wave reflection and the shape of the arterial pressure waveform. A detailed description of this methodology is provided by Rhodes and Suderland.[70] The recalibration interval recommended is 8 hours but more frequently in haemodynamic instability.[118]

Hamilton et al in their study involving 20 post coronary artery bypass graft patients compared this method with PAC thermodilution. They confirmed a good correlation and agreement based upon Bland Altman analysis.[119]

Jonas et al validated this method with Lithium dilution in their adult ICU patients. They showed a good agreement between the two with mean bias of 0.3 litres/min, with limits of agreement $\pm$ 1.7 litres/min and a percentage error of twenty one.[69]

Limitation of Pulse power analysis

The limitations associated with its use are in actual fact due to Lithium bolus dilution (calibration technique) rather than the actual pulse power analysis. It cannot be used accurately in patients on therapeutic Lithium therapy, is affected by plasma sodium concentration and is interfered with the concurrent use of depolarising muscle relaxants due to a drift caused in the lithium sensor.

(ii) Uncalibrated methods

a) Flo Trac/Vigileo system (Edwards Life Sciences, California, USA)

The Flo Trac/Vigileo measures CO in a continuous fashion without the need for any invasive manual calibration. The upgraded, second generation device is calibrated automatically every minute by assessing changes in arterial compliance based upon demographic data and the shape of the arterial pressure waveform. The algorithm makes an assumption that the pulse pressure is directly proportional to the stroke volume and considers the skewness and kurtosis of the arterial waveform. The arterial compliance and vascular resistance are estimated form patient demography. The arterial pressure waveform itself is analysed and averaged over twenty seconds and a beat detection algorithm eliminates extra -systoles and other small artefacts. Flo Trac/Vigileo can be easily connected to the already existing arterial catheter via its transducer for displaying CO.[120]

The studies involving first generation device had poor correlation and agreement with the reference standard methods.[121,122] This led to the upgrading of the software leading to second and third generation devices. However, Desebbe et al in their study involving adult cardiac surgical patients demonstrated inaccuracy of even the third-generation FloTrac/Vigileo software to reliably detect changes in cardiac output in cardiac surgery.[123]

Limitations specific to FloTrac/Vigileo method

(i) The algorithm may be of uncertain value in cases of rapid, extreme changes in haemodynamics, although it may still be useful as a trend monitor.[124]

(ii) Some authors have also demonstrated inaccuracies in measurement of CO in cases of vasodilatation with hyperdynamic circulation like sepsis [125] or hepatic cirrhosis.[126]

b) Pressure recording analytical method (PRAM, MostCare, Vytech, Padova, Italy)

PRAM is based upon the principle that volumetric changes in a blood vessel primarily occur in a radial direction influenced by the interaction between the left ventricular ejection force, arterial compliance, impedance and peripheral resistance to the flow . PRAM measures the area under the pressure curve of the arterial waveform for calculation of stroke volume. Though no external calibration is needed, it does require an internal calibration factor dependent upon the morphology of the waveform.[127] PRAM is a relatively new method; hence, there are very few comparison and validation studies available in the literature.

Calamandrei et al in their study involving 48 critically ill children compared PRAM with Doppler echocardiography for the measurement of CO. Cardiac output values obtained by Doppler echocardiography (2.7 +/- 1.6 litres/min, range 0.92-8.20) were significantly correlated with those estimated by PRAM (2.6 +/- 1.7 litres/min, range 0.89-7.48; r2 = .99, p < .01). The mean difference between the two estimates was 0.12 +/- 0.27 litres/min (95% confidence interval, -0.54 to 0.77 litres/min.[128]

However, PRAM requires further validation studies especially in paediatric patients in different clinical settings before it can be recommended for the measurement of CO reliably.

c) LIDCO rapid

This is based upon the same principle as LIDCO plus. However, it uses nomogram for estimation of calibration or patient specific correction factor for conversion of nominal stroke volume to the actual stroke volume. Thus, no calibration is required with Lithium chloride injection.

Comparison between calibrated and uncalibrated methods

Calibrated devices have not always shown benefits [129] but the majority of the available data points towards a better performance of the calibrated devices as compared to the uncalibrated monitors.

Hadian et al compared PiCCO, LiDCO plus and FloTrac with PAC thermodilution. They demonstrated larger bias and wider limits of agreement with FloTrac as compared to PiCCO and LiDCO.[130]

Similarly Cecconi et al compared LiDCO plus and FloTrac /Vigileo with PAC in critically ill patients with similar results as above.[131]

Summary of paediatric studies using pulse contour methods

A representative summary of studies utilising different pulse contour methods in children is presented below in table 1-5. Most authors showed an acceptable value of error to consider pulse contour methods in good agreement with either indicator dilution or Doppler techniques. Percentage error could not be calculated for study by Falker et al due to unavailability of the data (in the manuscript) however, the authors reported a good correlation between PiCCO and TPTD (r=0.93). Of note, Mahajan et al reported a percentage error of 54% while comparing pulse contour methods in children with congenital heart disease.[132] This may be explained by two important reasons. Firstly, presence of intra-cardiac shunts and valvular disease in some of their patients, may have affected the CO measurements. Secondly, authors chose to take pulse contour readings just before TPTD measurements to avoid capturing autocalibrated pulse contour readings every time TPTD measurements are taken.

Table 1-5 Summary of paediatric studies representative of using pulse contour methods

Author (year)	Technique	Ref.	N	Weight (kg)	CO (l/min/m^2)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Falker [117] (2007)	PiCCO	TPTD	24	10.6 - 35.6	1.86 -7.04	0.05	0.8	na$^+$	0.86
Mahajan [132] (2003)	PiCCO	TPTD	16	>10	1.4 - 9.7	0.08	1.98	54	0.53
Kim [133] (2006)	LiDCO Plus	TPLD	20	13 - 77	1.9 - 5.9	0.19	0.28	8.8	0.88
Calamandrei (2008) [128]	PRAM	TTE-Doppler	48	2 - 45	0.89 – 7.48 (non indexed) (l/min)	0.12	0.6	20.3	0.98

LOA = limits of agreement; N = number of subjects; na$^+$ = Not available; PATD = pulmonary artery thermodilution; PE = Percentage error; PRAM = Pressure recording analytical method; Ref.= Reference method; TOD = Transoesophageal Doppler; TTE = Transthoracic echocardiography; Weight and CO are expressed as range.

1.2.8 Bioimpedance, Bioreactance and Electrical velocimetry

(i) Bioimpedance

Bioimpedance technology uses constant electric current stimulation for identification of variations in electrical impedance associated with physiological (blood flow) or pathological changes (pulmonary oedema). A biological cell consisting of intracellular fluid, cell membrane and extra cellular fluid acts as resistor-capacitor while the blood vessels behave as electrical conductors. Kirchow's law states that the electric current passes through conduits of higher conductance. This will be across the blood vessels in a human body. Therefore, there is a proportional increase in the aortic electrical conductance with each systole due to an increase in the blood volume. Stroke volume is calculated from the following equation:

$$Stroke\ volume = \frac{VET \times dZ/dt\max \times L^3}{4.25 \times Z_0}$$

where
L: thoracic segment length
VET: ventricular ejection time
dZ/dt_{max}: maximum rate of impedance change and
Zo: transthoracic baseline impedance

Impedance (opposition to flow of alternating current) can be measured in the body by the help of a potentiometer. Placement of electrodes at the root of the neck and xiphisternum measures thoracic electrical bioimpedance (TEB). Whole body electrical bioimpedance (WBEB) is measured by placing the electrodes at the wrist and the contralateral ankle. Both TEB and WBEB can be used for measurement of CO. In TEB, there is transthoracic transmission of the electrical impedance variations due to the increase in blood flow through the pulmonary artery and aorta. In other words, the rate of change in TEB over time is proportional to the rate of change in aortic blood flow. In WBEB, the arterial blood to the peripherally placed electrodes transmits the impedance variation of the aorta.

Since the original work of Mann [134] and Kedrov [135] there have been alterations in the original formula (mentioned above) for the derivation of stroke volume. The most recent modifications have been by Kubicek, Sramek and Bernstein.[136-138]

Bioimpedance technology was compared with other methods for measuring CO including a meta-analysis in 1999. This compared bioimpedance with thermodilution and demonstrated a correlation coefficient of 0.67-0.71 in critically ill and healthy patients respectively. However, patients with cardiac pathology only demonstrated a correlation coefficient of 0.59. This is because of the high prevalence of pulmonary oedema, peripheral oedema or pleural effusion in this group of patients that will affect the measurement of impedance variations.[139]

Various other studies have demonstrated inconsistent and variable results.[140,141] Hence, its use has been recommended more towards trend analysis rather than diagnostic interpretation.

(ii) Bioreactance (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK)

This is a modification of bioimpedance technology to overcome the sources of potential errors. Four dual sensors (each dual sensor consists of an outer and an inner sensor) are applied on the chest wall of the patient. The device generates a signal at a frequency of 75 kHz into the thorax via the outer portion of the sensors. The signal is reflected from the base of the aorta back to the sensors, which is then compared to the original signal. Based upon the shift form the original signal called 'phase shift', or 'time delay, stroke volume is calculated. Bioreactance has been compared with Doppler [142] and thermodilution based techniques [143,144] with promising results.

(iii) Electrical velocimetry

This is a recent modification in the impedance algorithm. It is based upon the Bernstein–Osypka equation.[145] The principle is based on the theory that the change in the alignment of red blood cells from an arbitrary orientation in diastole to a parallel alignment in systole induces an increase in electrical conductivity of blood. SV is calculated by measuring this change. Standard ECG surface electrodes are placed side-to-side in a vertical direction to the patients' left middle and lower neck, and to the lower thorax at the left mid-axillary. Preliminary pediatric evaluation has proven to be promising when compared to Fick.[146]

A summary of paediatric studies utilizing bioimpedance and related techniques is presented in table 1-6.

Sources of error for bioimpedance based techniques

(i) The methods are extremely sensitive to electrode position and contact. Any perspiration or activity leading to loss of contact will interfere with accuracy of the monitor.

(ii) Changes in tissue water content (alteration of bioimpedance) due to tissue oedema, pleural effusion and pulmonary oedema leads to inaccurate results.

Summary of paediatric studies using bioimpedance and electrical velocimetry

Only a limited number of paediatric studies are reported in the literature about this method. They are summarised in table 1-6. Most demonstrated an unacceptable percentage error for agreement with the reference methods. The wide variation in limits of agreement is noticeable and may be due to variation in the reference methods or patient population (Pianosi et al: cystic fibrosis patients; Schubert et al: post cardiac surgical children; remaining two studies recruited children from cardiac catheter lab). Considering the wide variation in the results, larger well

designed studies are required to find the accuracy and precision of this particular monitoring device.

Table 1-6 Representative summary of paediatric studies with bioimpedance and electrical velocimetry

Author (year)	Technique	Ref.	N	Wt. range (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Pianosi [147] (1997)	EBI	CO_2R	21	21-87	na[+]	-0.09	1.84	na[+]	0.81
Norozi [146] (2008)	EV	O_2-Fick	32	2.7 – 54	0.4 - 4	0.01	0.46	na[+]	0.94 (r=0.97)
Schubert [148] (2008)	EV	TTE-Doppler	13	2.6 – 47	2.3 (SD1.4)	0.87	3.26	91*	0.77
Tomaske [149] (2008)	EV	PATD	50	0.5 – 16.5	0.6 - 7.2	0.66	1.49	43.8	0.79

CO_2R = Indirect Fick; EBI = Electrical bioimpedance; EV = Electrical velocimetry; LOA = limits of agreement; N = number of subjects; na = Not available; PATD = pulmonary artery thermodilution; PE = Percentage error; Ref. = Reference method; TOD = Trans esophageal Doppler; TTE = Transthoracic echocardiography; Weight and CO are expressed as range; * = calculated from graph/data in the manuscript; [+] = data not available even in the manuscript.

1.2.9 Other methods for measuring cardiac output

This section briefly describes other methods available for measurement of cardiac output. However, these techniques require further validation studies in adults and paediatric age groups in different clinical settings before gaining recommendation for routine clinical use.

(i) Photoplethysmography and the Volume clamp method (Nexfin, BMEYE, Amsterdam,The Netherlands)

Jan Penaz first developed the 'volume clamp' technique in 1967. This involved monitoring of the changes in arterial blood volume of a finger by an infrared transmitter and receiver combination, which is connected to an inflatable finger bladder and driven by a feedback control mechanism. The finger cuff is inflated and deflated to maintain a constant level of infrared absorption (or blood volume). When the artery is 'unstretched', the volume clamp technique assumes that the pressure in the finger cuff is equal to the arterial pressure. Thus, by maintaining the artery in an 'unstretched' form, finger pressure can be measured continuously. This peripheral arterial pressure waveform can then be used to estimate stroke volume using the methods described in the pulse contour analysis section.

This device has shown good agreement with invasive blood pressure monitoring system in adult [150,151] and paediatric settings.[152] However, it failed to show inter-changeability with other methods of CO monitoring in a limited number of reported studies.[153,154]

(ii) Pulse wave transit time (PWTT) (esCCO^{TM}, Tokyo, Japan)

PWTT is defined as the time measured from the ECG R-wave peak to the rise point of SpO2 pulse wave and consists of three time components. First is the pre-ejection period including the electromechanical delay at the start of systole and isometric contraction time with the R wave of

ECG serving as the starting point. Second is the time it takes for pulse wave to travel from the aorta through the elastic arteries to and lastly the time it takes for pulse wave to travel from the muscular artery to the further distal peripheral site of SpO2 measurement.

The esCCO monitor incorporates both PWTT (based on the ECG and pulse oximeter waveforms) and mean arterial pressure into its estimate of stroke volume and assumes a negative correlation between the stroke volume and PWTT.[155] Various studies have shown inconsistent results with the use of this device hence it has not found its use in widespread clinical settings.[156,157]

1.3 Animal and Adult experiments

Data from the animal studies provide a valuable adjunct to the assessment of CO monitoring devices in children and infants. Animal experiments offer three major advantages. First, the comparator method is often closer to a true gold standard. Typically, this comprises an invasive method such as ultrasound flow probes, which are placed around the aorta or the pulmonary artery. Theses provide a precision of 1% -2%. Second, the methods can be evaluated under extreme haemodynamic states such as shock (during haemorrhage), resuscitation or with artificial shunts. These conditions may be difficult to replicate in human subjects. Finally, animal subjects demonstrate physiological similarity with paediatric patients in terms of weight and circulatory volume. Hence, the initial animal data may prove useful when planning clinical validating studies.

Table 1-7 provides a narrative summary of key animal and human adult studies using different types of CO monitoring devices. Transpulmonary indicator dilution (thermal or ultrasound dilution) methods seemed to be accurate both in adults and animal studies when compared to reference methods such as ultrasound flow probes and pulmonary artery thermodilution. Indirect Fick has shown large errors in animal and adult experiments. Both these results are also reflected in paediatric studies (see Table 1-1 and 1-2).

Peyton et al [158] performed a meta-analysis of accuracy and precision of minimally invasive CO monitoring methods in human adults. They demonstrated, using pulmonary artery thermodilution as a reference method, a pooled percentage error of 41.3%, 42.1%, 44.5% and 42.9% with pulse contour, oesophageal Doppler, indirect Fick and electrical bioimpedance respectively.

Extrapolation of results from adult studies cannot be applied directly to paediatric patients. This could partly be due to unique vascular properties and haemodynamics as part of normal growth and various pathological states. This is very well demonstrated by pulse contour methods. Most studies have shown a better performance in adults as compared to the paediatric population (also see Table 1-5).

In summary, out of the various CO monitoring devices, indicator dilution devices are considered accurate for measuring CO in clinical practice but are slow to response and are invasive in nature. Pulse contour methods respond faster to changing clinical condition, however, are not validated to accurately measure CO in children. Ultrasound Doppler based methods are fast and responsive and have reported to be fairly accurate in their trending ability to monitor changes in CO.

However, good quality validation studies are still required for upcoming new and some of the established technologies specifically targeting paediatric practise. The challenge however remains in terms of funding, practicality and ethical considerations.

Table 1- 7: Summary of relevant animal and adult (human) studies assessing different methods of CO measurement

Author (year)	Technique	Ref.	Subjects	N	Wt. range (kg)	CO (l/min)	Bias (l/min)	LOA (l/min)	PE (%)	R^2
Fick method										
De Boode et al (2007) [159]	Modified CO2 Fick	UFP	Lambs	7	2.9-6.40	0.2-1.4	.08	0.25	35	0.86
Kotake et al (2003) [160]	Modified CO2 Fick	PATD	Humans	28	59±9	3.6±1.7	-0.52	0.95	46.3*	na
Indicator dilution methods										
Lemson et al (2008) [161]	TPTD	UFP	Lambs	11	4.2-12.5	0.4-3.1	0.2	0.24	14.7	0.95
Ruperez et al (2004) [162]	TPTD	PATD	Pigs	16	9-16	0.9-5.6	0.28	0.63	30	0.86
Piehl et al (2008) [163]	TPTD	PATD	Pigs	10	24-37	0.8-6	0.14	0.47	11.6	0.96
De Boode et al (2010) [164]	TPUD	UFP	Pigs	9	3.5-7	0.46-1.9	0.04	0.26	26.9	na
Segal et al (2002) [165]	TPTD	PAC	Humans (Adults)	22	27-79 (Age range in yrs)	6.56±1.57	0.27	1.34	21.6*	0.82
Staier et al (2012) [166]	TPTD	PAC	Post Mitral valve repair (Adults)	30	48-70 (Age range in yrs)	7.49±1.44	0.05	14.4 to -12.77	13.6	na
Pulse contour methods										
Lopez-Herce et al (2006) [167]	APCCO (PiCCO)	TPTD	Pigs	51	9-16	0.52-4.22	.04	1.1	62.7	0.41
Piehl et al (2008) [168]	APCCO (PiCCO)	PATD	Pigs	10	24-37	0.8-6	0.11	0.45	11	0.97
Goedje O et al (1999) [169]	PiCCO	PATD	Humans (Adults)	24	41-81 (Age range in yrs)	3-11.8	.07	1.4	1 (% diff.)	0.85
Oesophageal Doppler methods										
Critchley et al (2005) [170]	TCCWD (USCOM)	UFP	Dogs	6	11-22	0.9-5.6 (range)	-0.01	0.33	13	0.87
Hullett et al (2003) [171]	TOD	PAT	Humans (Adults)	20	37-74 (Age range in yrs)	na	-0.56	0.64	24.6*	0.38
Bioimpedance methods										
Osthaus et al (2007) [172]	EV	TPTD	Pigs	5	11.2-13.8	0.29-4.5 (range)	-0.63	1.28	83	0.67
Cotter et al (2004) [173]	WBEB	PAC	Humans (Adults)	122	NA	2.38	-0.0009	-0.6849 ±0.6831	28.6	0.79

APCCO = Arterial pressure based continuous cardiac output; CO_2R = Carbon dioxide rebreathe; EV = Electrical velocimetry; LOA = limits of agreement; N = number of subjects; na^+ = Not available; PATD = pulmonary artery thermodilution; PE = Percentage error; Ref = Reference method; TCCWD = Transcutaneous continuous wave Doppler; TPTD = Transpulmonary thermodilution; TOD = Transoesophageal Doppler; TTE = trans thoracic echocardiography; UFP = Ultrasound flow probes, WBEB = Whole body electrical bioimpedance; * = calculated from data

1.4 Expert Commentary and Summary

This chapter summarised commonly used CO monitoring devices used in different clinical settings. In addition to Shepard's[14] definition of an ideal CO monitor (see Table 1-8) and characteristics such as clinical validity, large signal to noise ratio, practicality of using a certain monitor plays an important part in choosing a monitoring device[174]. This is especially true since none of the available devices fulfil all the properties of an ideal CO monitoring device.

Hence, the following practical points are to be considered when choosing a particular device:

(i) Patient related factors such as age, presence or absence of invasive venous and arterial catheters, cardiac anatomy in terms of presence of shunts or valvular regurgitation and severity of haemodynamic instability.

(ii) Monitoring device: Firstly, differentiating whether the clinician is interested primarily in measurement of *absolute* values or tracking *changes* in CO in response to interventions. In the first case a more invasive approach is required where as a continuous monitoring device may be suitable for tracking purposes. Secondly, the degree of invasiveness which will be acceptable to the patient. Generally, less invasive monitoring devices are less accurate and less reproducible. Finally, the desirability for obtaining additional haemodynamic variables such as extra vascular lung water or arterial pressure variations.

(iii) Clinician experience or preference with any particular device and the clinical environment (ward, emergency department or intensive care settings).[175]

In summary, invasive dilution techniques are more appropriate for haemodynamic monitoring in pathologies such as severe septic shock or post-operative period where the child already has invasive catheters (venous and arterial) in situ while undergoing intensive care treatment. This may guide physicians in targeting appropriate therapy. Minimally invasive continuous CO monitoring using pulse contour devices or transoesophageal Doppler could prove useful in children in peri-operative periods as shown in adults. Non invasive methods such as transcutaneous Doppler technique, Echocardiography or bioimpedance based methods may be useful in the initial phases of treatment in critically ill children with limited venous or arterial access.

Whatever method is used or chosen, treating physician should have a good understanding of the advantages and disadvantages of the monitoring device and have the knowledge to interpret the data to utilise these monitors effectively in improving patient outcomes. In addition, ongoing research is required for validating newer methods and refining existing algorithms towards paediatric population. This is somewhat hampered by a lack of commercial interest and ethical and practical difficulties in performing such studies in small children.

Table 1-8 Characteristics of different CO monitoring devices based upon Shepard [14]

Method	Morbidity (Catheters)	Repeatability	Continuous or Intermittent	Response time	Operator dependence	Accuracy (Paediatrics)
Fick						
O_2 Fick	+ (A,C)	+	I	Slow	No	++
CO_2 R	-	+	I	Slow	No	+
Indicator dilution						
PATD	+++ (PAC)	++	I	Slow	Yes	++
TPTD	++ (A, C)	++	I	Slow	Yes	++
TPUD	++ (A, C)	++	I	Slow	Yes	+
TPLD	+ (A ± C)	++	I	Slow	Yes	+
Dye Dilution	+ (A, C)	++	I	Slow	Yes	+
Ultrasound methods						
TOD	+	+	C	Fast	Yes	±
TCD	-	-	I	Fast	Yes	+
Arterial pulse contour methods						
PiCCO (APCCO+TPTD)	++ (A, C)	+	Cont.	Fast	Yes (Calibration)	+
Pulse power (APCCO+ Li)	++ (A, C)	+	Cont.	Fast	Yes (Calibration)	+
Flo Trac	+ (A)	-	Cont.	Fast	No	±
PRAM	+ (A)	-	Cont.	Fast	No	-
Bioimpedance						
EBI	-	-	Cont.	Fast	No	-
EV	-	-	Cont.	Fast	No	-

+ Represents the degree of invasiveness or accuracy (+ to +++ represents increasing invasiveness or accuracy). A = Arterial catheter; APCCO = Arterial pulse contour continuous cardiac output; C = Central venous catheter; Cont. = Continuous; CO_2R = Carbon di oxide rebreathe; EBI = Electrical bioimpedance; EV = Electrical velocimetry; I = Intermittent ; PAC = Pulmonary artery catheter; PATD = Pulmonary artery thermodilution; PRAM = Pressure Recording Analytical Method; TCD = Transcutaneous Doppler; TOD = Transoesophageal Doppler; TTE = trans thoracic echocardiography; TPTD = Transpulmonary thrmodilutiom; TPUD = Transpulmonary ultrasound dilution; TPLD = Transpulmonary Lithium dilution.

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Chapter 2 - Review of:

(a) Static and dynamic markers of preload and fluid responsiveness commonly used in clinical practice

(b) Introduction to arterial dP/dt_{max} (maximum rate of rise of arterial pressure waveform) – a marker for left ventricular contractility.

2.1 Introduction

Haemodynamic instability secondary to intra-vascular volume depletion is extremely common in critically ill patients. Fluid resuscitation or volume expansion may allow restoration of ventricular filling, cardiac output and arterial pressure and is routinely used to improve haemodynamics in critically ill patients.[1,2] This improves oxygen delivery at the tissue level, a vital and important step in the management of critically ill patients.

An increase in stroke volume SV of ≥15% is regarded as a significant response to therapies aimed for augmentation of CO by most authors.[3] However, multiple studies designed for evaluating fluid responsiveness in critically ill patients demonstrated a response rate of only about 50% in terms of a significant increase in stroke volume or cardiac output.[4]

The response to fluid bolus administration predominantly depends upon two main factors (a) the position of the myocardium on the Frank-Starling curve with respect to cardiac preload and (b) ventricular contractility as described below.

Preload relates to the amount of passive ventricular wall stress (or tension) at the end of diastole.[5] Blood volume in the ventricles at the end of the diastole is the main determinant of cardiac preload. The SV will change with preload change on the ascending or steep part of the curve (marked as green rectangle in fig 2-1) as compared to on the flat part of the curve (marked as red rectangle in fig 2-1). The first situation is preload dependence where there is a gain in SV after fluid bolus administration and the latter situation is known as preload independence where any further increase in preload does not lead to any significant increase in stroke volume.

Ventricular contractility: the slope of the Frank-Starling curve is determined by ventricular function or contractility (fig 2-1). The curve becomes flatter (reduced slope) and shifts to the right with decreasing ventricular function. This is manifested as a reduction in the gain in stroke volume for the same amount of preload change (fig 2-1, see curves marked 1 and 5).

Recognition of both these factors is important, as volume loading at a stage of preload independence may be detrimental to the patient. It will lead to an increase in bi-ventricular diastolic pressure, which in turn has numerous negative consequences such as increase in ventricular wall tension, impedance of coronary flow, distortion of the ventricular septum with consequent alterations in the ventricular function, the production of peripheral oedema and compromised flow to the liver and kidneys.[6]

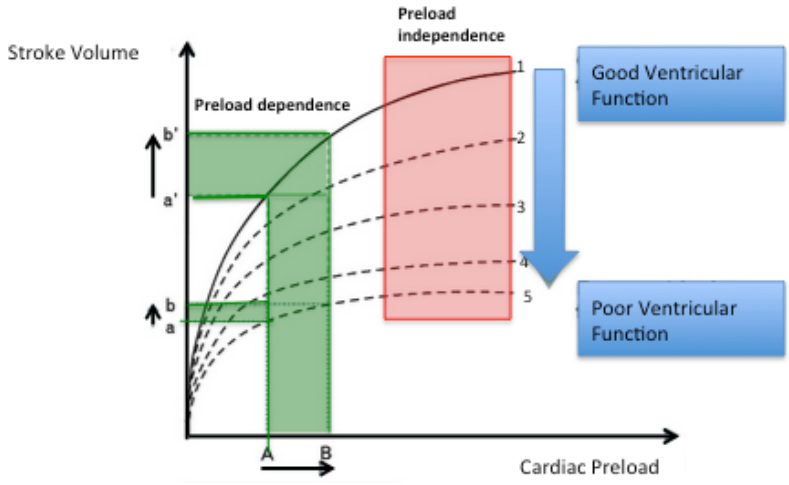

Figure 2-1 Frank-Starling curve.The green zone represents the region of fluid responsiveness whereas the red rectangle represents the area of preload independence. Magnitude of stroke volume change depends upon the myocardial contractility for similar increase in the preload. Here, curve 1 has good contractility demonstrating much greater increase in stroke volume (a' to b') as compared to the curve 5 with poor contractility having a smaller change in stroke volume from a to b, for the same increase in the preload from A to B.

This emphasises the requirement for an accurate assessment of patient haemodynamic status. However, various authors have demonstrated the inadequacy of clinical examination and routine monitoring for accurate assessment of haemodynamics.[7,8] This reinforces the need to search for accurate predictive markers of fluid responsiveness in order to select patients likely to benefit from volume expansion and avoid ineffective and deleterious volume expansion in non-responder patients where other treatment strategies should be employed.[9]

These markers are subdivided into static and dynamic markers. The section below describes some of the commonly used markers (including those measured by PRAM and TPUD) for predicting fluid responsiveness in clinical practice. The chapter also highlights general and specific sources of error and limitations associated with these markers. A representative

summary of paediatric studies evaluating the utility of these markers in prediction of fluid responsiveness is also presented at the end of each section.

2.3 Static markers

Static markers are single measurements essentially based upon direct or indirect estimates of ventricular filling. Various authors have suggested estimation of either the ventricular area (left ventricular end diastolic area), blood volume (global end diastolic volume, intra-thoracic blood volume) or pressure based parameters (central venous pressure, pulmonary artery occlusion pressure) as representative of preload estimation. Over the past few years, a large number of studies have explored the utility of these static markers for the prediction of response to fluid bolus administration.

The potential advantages for measuring static markers are:
(i) Independence from the cardiopulmonary interactions during mechanical ventilation,
(ii) They can be measured in patients with arrhythmias and
(iii) Finally, they do not require muscle relaxation for accurate measurements, in contrast to the dynamic markers.

None of these however, as yet, have convincingly proved to be useful for this role in critically ill paediatric patients.

Transpulmonary ultrasound (TPUD) provides three novel volume based static markers: total end diastolic volume index (TEDVI), central blood volume index (CBVI) and active circulating volume index (ACVI). There are no studies reported to date regarding the utility of these markers for the purpose of predicting fluid responsiveness. My study has investigated the role of these three markers for prediction of response to fluid bolus administration in critically ill children.

This section provides a description of commonly measured static markers used in clinical practice including the three novel static markers measured by the TPUD technique.

Description of commonly used static markers

(i) Central venous pressure (CVP)

CVP is defined as the pressure of the blood in the thoracic vena cava near the right atrium. It is essentially equivalent to the pressure in the right atrium assuming no venacaval obstruction .[10,11] The origins of the CVP monitoring can be traced back to Hughes and Magovern [12] in 1959, where they described a technique for monitoring right atrial pressure as a guide to blood volume replacement in post-thoracotomy patients. Wilson and Grow [13] further popularized its use.

CVP depends upon the interaction between cardiac function and factors determining venous return to the heart. Body fluid volume, venous capacitance, venous compliance, heart rate, rhythm, structural defects of the heart, pericardial effusion or tamponade are some of the major factors.[14] The range of normal value quoted in the literature is fairly wide with typical values, referred to the mid-axillary line as 2-10cm H_20.[15]

Studies evaluating the use of CVP for prediction of fluid responsiveness in adult patients

CVP has been used frequently to guide fluid management in intensive care settings.[16] Marik et al [17] in their systematic review of 24 studies (803 adult patients) demonstrated a very poor relationship between CVP and blood volume. In addition, they reported the inability of CVP/ΔCVP to predict response to a fluid bolus administration. Other authors have also reported similar conclusions.[18-20]

Paediatric studies evaluating the use of CVP for prediction of fluid responsiveness

Various authors have evaluated CVP for fluid responsiveness in paediatric population. The range of area under the ROC curve (AUC) ranged from 0.47 [21] to 0.69 [22], thereby demonstrating the inability of CVP to accurately predict fluid responsiveness in children (see table 2-1)

Table 2-1 Summary of selective studies evaluating CVP for fluid responsiveness

Author (year)	N	Weight (kg)	Setting	AUC
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR Mean (SD)	Neuro OR	0.47
Renner [22] (2012)	26	9.7(4.3) Mean (SD)	Cardiac OR	0.69
Choi [23] (2010)	21	12(4) R, NR Mean (SD)	Cardiac PICU	0.48
Tran [24] (2007)	44	2.2 – 71.5 (Range)	Cardiac OR	0.58
Tibby [25] (2001)	94	3 – 60 (Range)	Mixed PICU	0.57

AUC = Area under the ROC curve; N = Number of fluid boluses administered; NR = Non responders; OR = Operating room; PICU = Paediatric intensive care unit; R = Responders.

(ii) Left ventricular end diastolic area (LVEDA)

The LV end diastolic area measured by transoesophageal echocardiography (TOE) in the trans-gastric, mid-papillary, short axis view has been used as a measure of preload in critically ill patients.[26,27] LVEDA is commonly estimated using a modified Simpson's rule, which assumes that the mitral and papillary muscle levels trisect the ventricle equally and the relative position and/or geometry of the involved planes is constant in systole and diastole.

Sources of error or limitations

(i) The estimation of LVEDA by TOE is an invasive procedure. Moreover, the trans-gastric views require a high level of expertise. This also makes it less suitable in practical situations during resuscitation of severely ill children.

(ii) The variability in LV geometry can be either age-related or due to different pathological states such as congenital heart disease, regional wall abnormalities. This limits the application of modified Simpson's rule for an accurate estimation of LVEDA.[28]

(iii) The pressure volume loops of the LV and RV may shift due to changes in myocardial relaxation, stiffness and systolic performance. Thus, a given ventricular volume may equate to different intra ventricular pressure depending on the interplay of the above factors. Hence, the estimation may become inaccurate and erroneous.

Adult studies evaluating the use of LVEDA for prediction of fluid responsiveness

Feissel et al in their study involving nineteen septic shock patients in adult ITU demonstrated that baseline LVEDA did not correlate significantly with the volume expansion-induced changes in cardiac index ($p= 0.17$) and was of little value in predicting the effects of volume expansion on cardiac output.[29] Other authors have also reported similar findings in adult patients.[30,31]

Paediatric studies evaluating the use of LVEDA for prediction of fluid responsiveness

Reich et al initially showed promising results in monitoring cardiac filling changes in paediatric patients by measuring changes in LVEDA.[32] However, LVEDA has shown to be a poor predictor of fluid responsiveness in both paediatric and adult settings in subsequent studies. de Souza Neto et al [33] studied the utility of LVEDA as a marker of fluid responsiveness in thirty mechanically ventilated children. The area under the receiver operating curve (AUC) was 0.59 (0.35–0.81) for children between 0-6 years. The AUC was slightly better for children between 6-14 years 0.71 (0.39–0.93) but still unsuitable to discriminate between responders and non-responders (see table 2-2).

Table 2-2 Representative summary of paediatric studies evaluating LVEDA for fluid responsiveness

Author (year)	N	Weight (kg)	Setting	AUC
de Souza Neto [33] (2011)	19	11(2) Median (MAD)	Neuro OR	0.59
de Souza Neto [33] (2011)	11	32(8) Median (MAD)	Neuro OR	0.71
Reich [32] (1993)	11	3 – 15 (Range)	Cardiac OR	na

AUC = Area under the ROC curve; MAD = Median absolute deviation; N = Number of fluid boluses administered; na = data not available; OR = Operating room.

(iii) Global end diastolic volume (GEDV) and Intra-thoracic blood volume (ITBV)

Ventricular preload is determined by an interplay between end diastolic pressure, ventricular wall thickness and radius of the ventricular cavity. Blood volume at the end of the diastole is the predominant factor affecting preload and is clinically best estimated as the end diastolic ventricular volume (EDV).

Global end diastolic volume (GEDV)

GEDV is the volume of all the chambers of the heart at the end of the diastole. It is estimated by a 'thermal' indicator dilution technique and is the difference between the intra thoracic thermal volume (ITTV) and pulmonary thermal volume (PTV).[34]

$$GEDV = ITTV - PTV$$

where
GEDV: global end diastolic volume
ITTV: intra thoracic thermal volume
PTV: pulmonary thermal volume

The estimation of ITTV and PTV is briefly described below.

ITTV is estimated by a transpulmonary indicator (thermal) dilution technique (see Chapter 1, section 1.2.2, page 31). This requires an injection of a cold indicator (≤10°C) through a standard central venous catheter into the right atrium or superior venacava with simultaneous measurement of the temperature dilution curves in the abdominal aorta or femoral artery using a thermistor tipped arterial catheter. The thermal bolus distributes throughout the entire thoracic vascular and extravascular compartment (intra-thoracic thermal volume, ITTV). The resulting dilution curve exhibits mono-exponential decay. Extrapolation of the decay curve to the baseline

from just before the point of recirculation by semi-logarithmic conversion enables calculation of the area under the curve, hence CO (see Chapter 1, section 1.2.2).

The volume of distribution for the thermal indicator is a function of CO and mean transit time (MT_t). Mean transit time is the time taken for detection of 50% of the amount of injected indicator by the distal thermistor; in other words, the centre of mass of the dilution curve area if recirculation is ignored (fig 2-2). Down-slope time (DS_t) refers to the rate of decline of the thermodilution curve which is estimated as the time taken for the semilogarithmic concentration curve to decrease by a factor of e^{-1} . This typically approximates a concentration drop from 85% to 45% of the peak of temperature change. The concept of using DSt for calculation of PTV was first described by Newman et al [35] and later reviewed by Isakow and Schuster.[36]

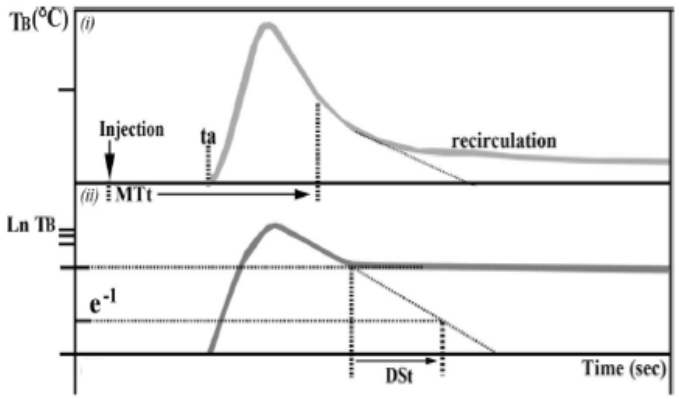

Figure 2-2 Calculation of GEDV. **Top panel**: 'Y' axis represents the concentration of the thermal indicator i.e 'temperature of the blood'. 'X' axis is time. 'ta' is the time delay between the injection of the cold saline and the onset of temperature sensing at the distal site. Extrapolation of the downslope corresponds to a first-pass effect of temperature variation that would have been obtained in the absence of any recirculation. **Lower panel** is the natural log (Ln) transformation of the transpulmonary thermodilution curve in the upper panel DSt: down-slope time refers to the decline of the thermodilution curve which is estimated as the time included within 85% and 45% of the peak of temperature variation.Reproduced from: Proulx et al. Paediatr Crit Care Med 2011; 12:45—466.[37]

$$ITTV = CO \times MT_t = GEDV + PBV + EVLW$$

where

ITTV: intra thoracic thermal volume
CO: cardiac output
MT_t: mean thermal transit time and is equal to the time taken for detection of 50% of the amount of injected indicator by the distal thermistor
GEDV: global end diastolic volume
PBV: pulmonary blood volume
EVLW: extra vascular lung water

Pulmonary thermal volume (PTV) is the sum of pulmonary blood volume and extra vascular lung water (fig 2-3). It is calculated with the use of the following formula:

$$PTV = PBV + EVLW = CO \times DS_t$$

where
PTV: pulmonary thermal volume
PBV: pulmonary blood volume
EVLW: extra vascular lung water
CO: cardiac output
DS_t: down-slope time (DS_t) refers to the rate of decline of the thermodilution curve, which is estimated as the time included within 85% and 45% of the peak of temperature variation (fig 2-2)

DSt corresponds to the volume of blood contained between proximal and distal thermal sensors, i.e., the sum of blood contained within the serial chambers: SVC, right atrium, right ventricle, pulmonary blood volume (PBV), left atrium, and left ventricle and aorta.

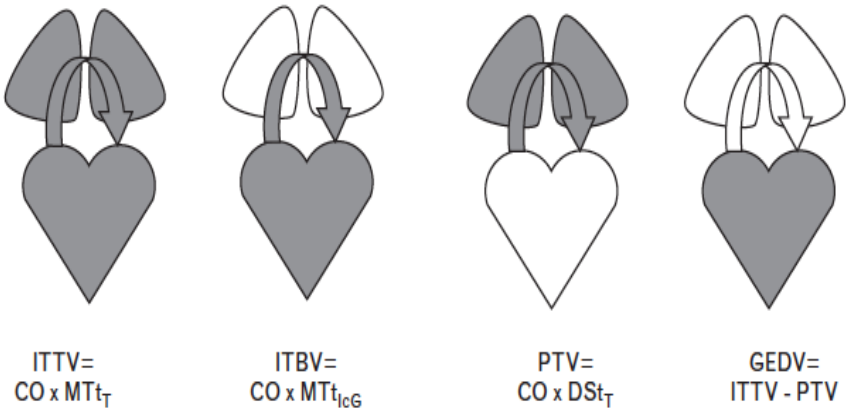

Figure 2-3 GEDV and ITBV estimation using an indicator dilution method. GEDV is the difference between Intra thoracic thermal volume and Pulmonary thermal volume. ITBV is measured using Indocyanine Green or can be estimated from GEDV(see text). Reproduced from: Benington S et al. European Journal of Anaesthesiology 2009; 26(11): 893-905. [34]

Limitations for measurement of GEDV

(i) Measurement of GEDV is by indicator dilution technique, hence, it has similar limitations and sources of error as a thermodilution or dye dilution technique such as indicator loss, recirculation and inaccuracies in patients with valvular regurgitation. These are explained in detail in chapter 1.

(ii) GEDV is not an accurate assessment of actual cardiac volume. It also includes blood volume in the vessels from the site of injection to the sensor. This is variable rather than a fixed volume due to changes in the venous and arterial mechanics in different pathological states.

(iii) Changes in the aortic elastance attributable to vasopressors (apart from dobutamine) may theoretically modify the GEDV without changing the true preload.[38,39]

Studies evaluating the use of GEDVI for preload estimation and/or prediction of fluid responsiveness in adults

Godje and co-workers performed a study about relationship between changes in SV with different preload markers in patients with heart transplantation. They demonstrated GEDVI was significantly correlated with changes in SVI (r= 0.73, respectively) in contrast to CVP and pulmonary artery occlusion pressure (r = -0.23 and r = - 0.06, respectively).[40] Sakka et al reported similar results in their study involving 57 adult ICU patients). GEDV was an accurate assessment of preload but was not able to predict fluid responsiveness.[41]

Paediatric studies evaluating the use of GEDV for prediction of fluid responsiveness

De la Oliva studied the utility of GEDVI for fluid responsiveness in 75 children subdivided into groups with normal cardiac function, cardiovascular dysfunction and dilated cardiomyopathy. Each of these patient groups were divided into subgroups with four different preload levels based upon GEDVI/$GEDVI_N$ ratio ['normal' GEDVI value ($GEDVI_N$) = 488.8 x (Body surface area)$^{0.388}$].The highest predicted responsiveness was observed in cardiac dysfunction patients with GEDVI less than or equal to 0.67 times normal global end-diastolic volume index (AUC of 0.89). The least AUC was observed in dilated cardiomyopathy patients with a GEDVI/$GEDVI_N$ ratio greater than 1.33 but less than or equal to 1.51 (AUC 0.52).[42]

Renner et al also investigated the role of global end diastolic volume index (GEDVI) in paediatrics for prediction of fluid responsiveness. They demonstrated a failure of GEDV to accurately predict fluid responsiveness in neonates and infants with intra-cardiac left to right shunts during pre-surgical setting (AUC 0.59). However, prediction after correction of shunts (closure of ASD and VSD shunts) was better with an AUC of 0.77 possibly due to improved accuracy of GEDV estimation.[22]

A summary of these studies is presented in table 2-3.

Table 2-3 Paediatric studies evaluating GEDVI for prediction of fluid responsiveness

Author (year)	N	Weight (kg) Mean (SD)	Setting	AUC
De la Oliva [42] (2015)	66	na	Mixed PICU	0.52-0.89*
Renner [22] (2012)	26	9.7 (4.3)	Cardiac OR (pre-op ASD/VSD)	0.59
Renner [22] (2012)	26	9.7 (4.3)	Cardiac OR (post-op ASD/VSD	0.77

AUC = Area under the ROC curve; ASD = Atrial septal defect; N = Number of fluid boluses administered; na = not available; OR = Operating room; VSD = Ventricular septal defect.

* includes patients with cardiomyopathy and cardiac dysfunction with four different preload levels classified according to GEDVI/GEDVI$_N$ ratio. GEDVI$_N$ = 488.8 x (Body surface area)$^{1.388}$.

Intra thoracic blood volume (ITBV)

ITBV is defined as the volume measurement of the left and right side of the heart along with the pulmonary blood volume at the end of diastole [43] (fig 2-3).

ITBV was initially estimated by a transpulmonary double indicator (thermal dye) dilution technique. An injection of cold Indocyanine Green (IcG) dye is injected into the right atrium or superior venacava. The temperature and IcG dilution curves are measured simultaneously in the abdominal aorta. The volume of distribution for each of the indicators (dye and cold) is a function of CO and mean transit time (MTt) (explained above).

Although the 'thermal bolus' distributes throughout the entire fluid compartment (intra-thoracic thermal volume, ITTV), the volume of distribution of IcG (highly protein bound) is limited to the intravascular compartment alone. This gives an estimate of ITBV (fig 2-3).

$$ITBV = CO \times MT_{ICG}$$

where
ITBV: intra-thoracic blood volume
CO: cardiac output
MT_{ICG}: mean transit time for indocyanine green and is equal to the time taken for detection of 50% of the amount of injected indicator distally.

Limitations for measurement of ITBV

(i) The limitations or sources of error for measurement of ITBV are similar for the measurement of GEDV. In addition to commercial unavailability of IcG, the method is expensive, time consuming and too cumbersome for bedside use.[34]

To overcome some of these shortcomings, different methods became available for its estimation with good correlation: transpulmonary single indicator (thermal) dilution technique [36, 41, 44] and contrast magnetic resonant imaging.[45] ITBV derived from single thermo dilution showed good agreement with the ITBV measured directly by double-indicator technique with a mean bias of 7.6(ml/m^2) and a standard deviation 57.4ml/m^2 .[46]

Sakka et al derived the following equation by using structural regression analysis to estimate ITBV by single thermodilution technique.[41]

$$ITBV = (1.25 \times GEDV) - 28.4(ml); r = 0.96, p < .0001$$

Of note, these were adult patients with minimum GEDV and ITBV values approximately 750ml and 800ml respectively on the structural regression analysis. This relationship may not hold true in children as the volumes are much smaller as compared to the adults.

(ii) Estimation of ITBV is partially based upon cardiac output (ITBV= CO x MTtIcg) hence, mathematical coupling between the two may seem possible. However, various authors demonstrated that infusion of dobutamine increased the CO [43,47] while esmolol decreased the CO [48] without any influence on thermodilution measurements of ITBV.

Studies evaluating the use of ITBV for preload estimation and/or prediction of fluid responsiveness in adults

Both Godje et al and Sakka et al [40,41] demonstrated ITBVI to be significantly correlated with changes in SVI (r =0.65), as compared to CVP and PAOP (r = -0.23 and r = - 0.06, respectively) and an accurate measure of cardiac preload. However, Muller et al in their study involving 35 patients with acute cardiovascular failure demonstrated ITBVI (Intra thoracic blood volume index) was unable to predict fluid responsiveness reliably (AUC 0.64).[49]

There are no paediatric studies evaluating the utility of ITBV for prediction of response to fluid bolus administration.

(iv) Static markers measured by the ultrasound dilution method

Transpulmonary ultrasound dilution technique is an indicator dilution technique using normal saline as an indicator. It estimates three volume based novel static markers: total end diastolic volume index (TEDVI), central blood volume index (CBVI) and active circulating volume index (ACVI).

At the time of initiating this MD, there were no reported studies evaluating the usefulness of these indices for predicting fluid responsiveness in critically ill children.

(a) Total end diastolic volume index (TEDVI)

This is the total amount of blood in the chambers of the heart at the end of diastole (see fig 2-4). The manufacturer recommends TEDV to be normalized to body weight for children weighing less than 40 kg (normal range being 7-12 ml/kg) and normalized to body surface area for more than 40 kg (expected range is 250-350ml/m^2).

Several authors have demonstrated inconsistencies in reported that cardiac volumes across childhood ages when scaled to body surface area (BSA) expressed in m^2. They are more closely related to $BSA^{1.38}$ rather than BSA alone.[50-52] This is in contrast to a more constant range of cardiac index scaled consistently to BSA (m^2). This is because changes in the heart rate (inverse relationship with BSA) and stroke volume (linear relationship with BSA) 'cancel each other out'. Hence, volumetric data (for TEDVI) was allometrically scaled to body surface area using a power of 1.38 (i.e. $(m^2)^{1.38} = m^{2.6}$) in our research study. Therefore, TEDVI volumes are expressed as $ml/m^{2.6}$.

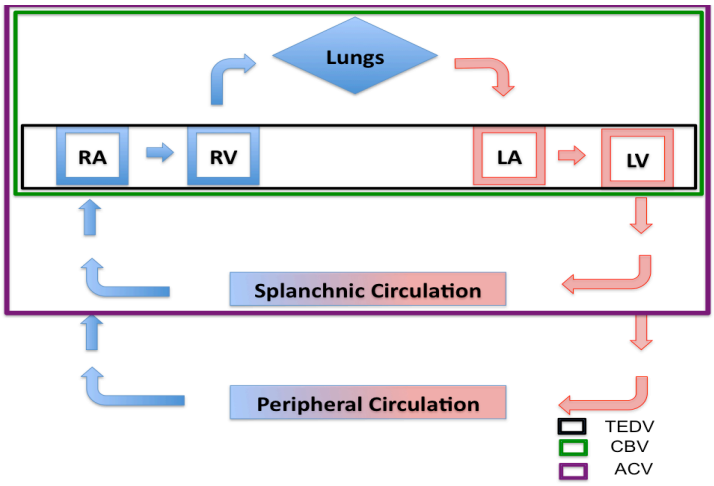

Figure 2-4 Static markers measured by TPUD.

Calculation of TEDVI assumes that the spread of the arterial indicator dilution curve from its initial venous shape results largely from indicator mixing in the heart chambers. TEDVI values may be unreliable in patients with left to right or right to left shunts.

TEDVI has shown to be an accurate reflection of the blood volume status. Vigani et al in their juvenile animal model demonstrated TEDVI to accurately reflect blood volumes during haemorrhagic and resuscitative phases. It was not affected by noradrenaline infusion. TEDVI also correlated with volume induced changes in stroke volume which was unaffected by noradrenaline infusion.[53] TEDVI can be considered as analogous to global end diastolic volume (measured by PiCCO), which has been assessed as a preload marker by various authors.[54,42] However, TEDVI is considered a more accurate reflection of cardiac chamber volumes as

compared to GEDVI, as the estimation of the latter includes the blood volume in the vessels between the site of injection and the sensor.

(b) Central blood volume index (CBVI)

This is defined as the total volume of blood in the heart, lungs and major vessels (fig 2-4).

CBVI is estimated by measuring the volume of blood between the injection and the recording (arterial) site and normalized to body weight. The longer the indicator travels, the larger will be the value of CBVI.

$$CBV = CO \times (MTTa - MTTv - MTTt)$$ [see fig 2-5]

where

MTTa: mean transit time of indicator traveling from the injection site (venous senor) to the arterial sensor

MTTv: mean transit time of the venous injection recorded by the venous sensor

MTTt: mean transit time that the indicator travels in the arterial loop before reaching the sensor

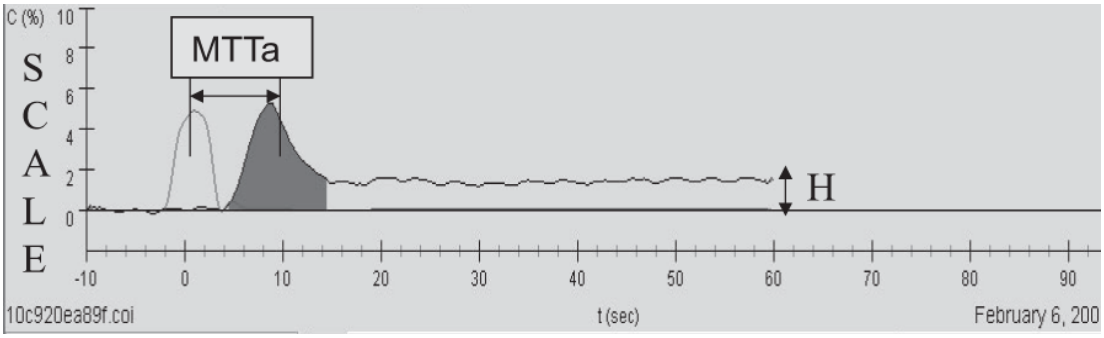

Figure 2-5 Screen shot from TPUD monitor. 'Y' axis is the percent concentration of saline in blood. 'X' axis represents time. The concentration of injected saline becomes stable with in 40-60 seconds from the time of injection (H) (with permission form Transonic, NY, USA).

The normal range of TEDVI is between 18-22 ml/kg. Eremenko et al demonstrated CBVI and TEDVI to be useful indicators of preload in adult patients admitted to the cardiac ITU.[55]

Crittendon et al in their study involving 22 children demonstrated CBVI and TEDVI could be used as novel preload markers. They showed good correlation between these two indexes with pulmonary artery wedge pressure and CVP.[56]

(c) Active circulating volume index

This is the volume of blood in which the indicator (normal saline) mixes within one minute after injection (see fig 2-4). This is indexed to body weight irrespective of the child's weight. The normal expected range is 40-60ml/kg. In smaller children <5 kg it may reach up to 75 ml/kg.

$$ACV = Vinj \div (H \times Weight)$$

where
Vinj: volume of injected isotonic saline (ml)
H: new level of isotonic saline concentration in blood [ml (saline)/ml (blood)] at the end of the first minute after venous injection as recorded by the arterial sensor (see fig 2-5).

Sources of error or limitations of ultrasound dilution method

(i) Being an indicator dilution technique, TPUD shares the same sources of error and limitations as other indicator dilution methods. Invasiveness, intermittent nature and slow response time are few of the examples. In addition, accuracy of these markers to estimate preload in children still needs validating, especially in the presence of anatomical shunts.

(ii) TPUD is as much prone to indicator loss errors as any other indicator dilution techniques. Though the venous sensor accurately measures the volume of the indicator injected however, the loss may be due to multiple other reasons past the venous sensor for example dead space of the venous catheter or abnormal lung perfusion.

(iii) Each measurement involves injection of normal saline as an indicator. This may result in a significant cumulative amount affecting fluid balance specifically in small babies.

A summary of studies involving these markers is presented in table 2-4. Note that none of these markers were evaluated for fluid responsiveness.

Table 2-4 Summary of studies evaluating various markers measured by TPUD for preload estimation

Author (Year)	Marker	Reference	Subjects (n)	Correlation
Vigani [53] (2012)	ΔTEDVI	ΔSVI	Animals (12) (ponies)	0.67
	Δ ACVI			0.25
	Δ CBVI			0.18
Eremenko [55] (2007)	ΔTEDVI	ΔSVI	Adult, Cardiac (15)	0.48
Crittendon [56] (2010)	CBVI	CI	Children (22)	0.58
	TEDVI			0.62

Δ ACVI = Change in active circulating volume index; CI = Cardiac index; CBVI and Δ CBVI = Central blood volume index and corresponding change post intervention respectively ; SVI and ΔSVI = Stroke volume index and corresponding change post intervention respectively; TEDVI and ΔTEDVI = Total end diastolic volume index and change respectively post intervention. Interventions are CO augmentation therapy such as fluid or inotropes.

2.2 Dynamic markers

Dynamic markers are a result of cardiopulmonary interactions resulting in cyclical changes of the loading conditions of the right and left ventricle as a result of mechanical ventilation (see section 2.2.1) . The magnitude of such respiratory-induced changes in the left ventricle (LV) stroke volume (further accentuated during hypovolaemia) can be measured and used to predict fluid responsiveness.[57] Pulse pressure variation (PPV), systolic pressure variation (SPV) and stroke volume variation (SVV) are some of the dynamic markers which are measured on a beat-to-beat basis by pulse contour based technology. These markers are relatively well evaluated in adult practice, however paediatric utility was not established at the time of commencement of my thesis. We studied the utility of these markers measured by PRAM in a cohort of 100 critically ill children.

2.2.1 Effects of positive pressure ventilation on ventricular function

Intermittent positive pressure ventilation induces cyclical changes in the loading conditions of both sides of the heart. Positive pressure ventilation leads to a reduction in right ventricular (RV) preload, due to a decrease in the venous return pressure gradient as a result of increased pleural pressure.[58]

The effect of mechanical ventilation on RV afterload is variable and depends upon interplay between a variety of factors described below:

(a) Effect of an increase in transpulmonary pressure: positive pressure ventilation increases trans alveolar pressure (alveolar – pleural pressure) affecting the blood vessels surrounding the alveoli.[59] This contributes towards an increase in afterload.

(b) State of the lung inflation: pulmonary vascular resistance (PVR) is lowest at functional residual capacity. Lung volumes higher or lower than the functional residual capacity will lead to an increase in PVR, hence the afterload.

(c) Phase of inspiration: The resistance values are consistently different during deflation (higher) and inflation (lower) at equal transpulmonary pressures.[60]

(d) Pulmonary artery flow: The flow resistance is lower at high pulmonary artery flow than at low flow state.[60]

(e) Mode of ventilation: positive or negative pressure ventilation has different effects on PVR for maintenance of similar lung volumes by Petak et al demonstrated an increase in PVR during positive pressure ventilation as compared to negative pressure for similar changes in lung mechanics such as airway resistance and parenchymal elastance.[61] Therefore, the net effect on RV afterload is variable and difficult to predict accurately in clinical settings.

Despite the variability on RV afterload, inspiration during mechanical ventilation typically leads to a reduction in RV stroke volume, with reduction in preload being the major contributor for this reduction [62] (fig 2-6).

Left ventricle is also subject to volumetric effects during the positive pressure inspiration. Mechanical insufflation may induce a squeezing of the blood out of the alveolar vessels and transiently increase the LV preload.[63] There is also a decrease in LV afterload due to reduction in the wall tension as a result of decline in transmural pressure, facilitating LV ejection.[64] These two mechanisms induce an increase in the LV stroke volume during the inspiratory period. The inspiratory decrease in the RV stroke volume leads to a decrease in the LV filling after a phase lag of two to three heart beats because of the long blood pulmonary transit time.[65] This leads to a decrease in LV ejection volume during the expiratory phase (fig 2-6).

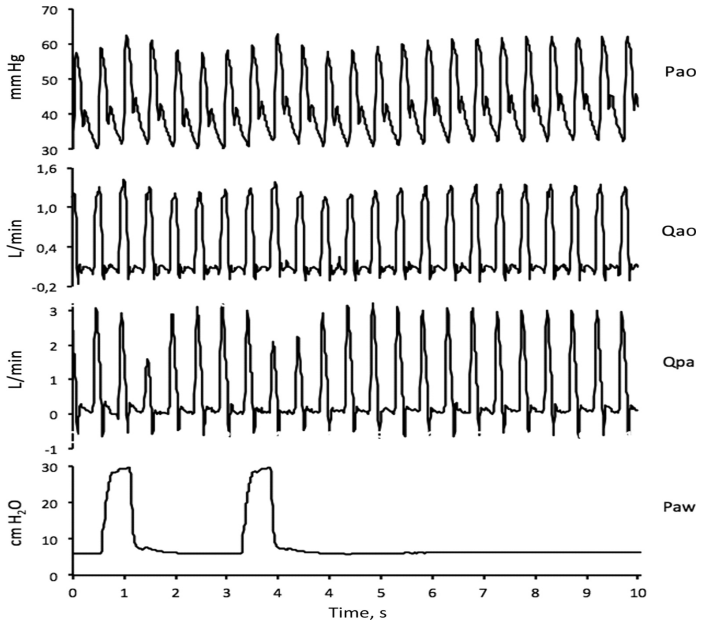

Figure 2-6 Arterial pressure variations during mechanical ventilation and subsequent apnoea. Note the fluctuations in the blood flow in pulmonary artery and aorta during inspiration and expiration. Qao = aortic blood flow; Qpa = pulmonary blood flow; Pao = arterial pressure in aorta; Paw = airway pressure. Reproduced from: Lemson J et al. Pediatrics. 2011 Sep;128(3):560-71.[66]

These cyclical changes are greater when the ventricles operate on the ascending portion of the Frank-Starling curve.[67] Thus, the magnitude of these changes in the LV stroke volume could be representative of an individual's preload dependence.[68]

2.2.2 Measurement of Dynamic markers

Dynamic indices were initially calculated manually using graphical analysis of arterial pulse waveform over a single respiratory cycle using mathematical equations. However, recently new software has been developed and validated to calculate these indices automatically and continuously from the arterial pressure waveform.[69,70] These algorithms were further improved in order to make it more robust during periods of abrupt haemodynamic changes.[71] In addition, non-invasive estimation of PPV using respiratory variations in the pulse-oximeter plethysmographic waveform amplitude has recently been evaluated with promising results.[72,73]

The following section describes commonly used dynamic markers for prediction of fluid responsiveness in clinical practice. General sources of error or limitations applicable to these markers are described at the end of this section. Errors or limitations unique to a particular marker are mentioned along with that specific marker.

2.2.3 Description of commonly used dynamic markers

(i) Systolic pressure variation (SPV)

The difference between the maximum and minimum systolic pressures divided by their average obtained during one mechanical breath is called the systolic pressure variation [74] (fig 2-7).

$$SPV = \frac{SAP\max - SAP\min}{\frac{1}{2} \times (SAP\max + SAP\min)}$$

where

SAP max and SAP min are the maximum and minimum systolic arterial pressure over one respiratory cycle.

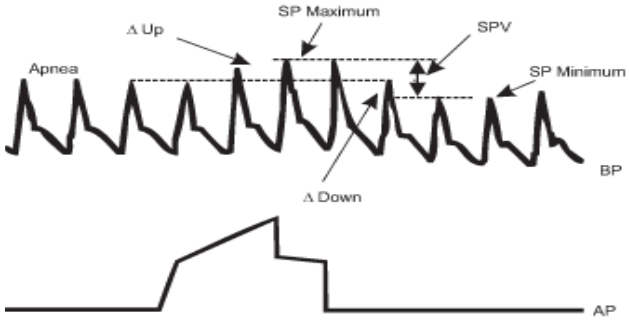

Figure 2-7 Systolic pressure variation. Note Δ Down and Δ UP in relation to the baseline pressure measured during apnoea. Reproduced from: Vieira CR, et al. Brazilian Journal of Anesthesiology, 2005; 55: 1: 3 -18.[75]

SPV (normally 8-10 mm of Hg) is composed of two different segments Δ Down and Δ UP in normotensive anaesthetized mechanically ventilated patients with SAP at end expiration as a reference.[74,76]

Δ Down (6-8 mm of Hg) is a decrease in the SAP during the expiratory phase reflecting the inspiratory decrease in preload to the right side of the heart being subsequently transmitted to the left ventricle several beats later.

ΔUP (3-4 mm of Hg): It is an early inspiratory increase in the SAP as a result of augmentation of stroke volume mainly caused by the increased preload to the left ventricle. In case of congestive heart failure, Δ UP may also be significantly contributed by the decreased afterload to left ventricle as a result of increased intra-thoracic pressure.[77,78]

Being purely related to preload ΔDown is considered a better marker as contrast to ΔUP. It is also considered to be the major contributor towards SPV.[79]

Studies evaluating the use of SPV for fluid responsiveness in adult patients

Travernier et al evaluated the ability of ΔDown to predict an increase in cardiac index after volume loading in 16 patients with sepsis. They demonstrated that Δ Down of 5 mm of Hg was a more accurate predictor of increase in cardiac index as compared to pulmonary artery occlusion pressure or left ventricular end diastolic area.[80]

On the contrary, Buettner et al in their study involving eighty patients undergoing major abdominal surgery showed that intra-operative SPV guided treatment was associated with slightly greater fluid administration with no difference in organ perfusion and function.[81]

Summary of paediatric studies evaluating the use of SPV for fluid responsiveness

Various authors have reported the inability of SPV to predict fluid responsiveness in children. A synopsis of these studies is presented in table 2-5. The maximum predictive ability for SPV in children is reported by Tran et al in their study involving 44 children in cardiac operating theatre (AUC 0.74).[24]

Table 2-5 Representative summary of paediatric studies evaluating the use of SPV

Author (year)	N	Weight (kg)	Setting	AUC
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR Mean (SD)	Neuro OR	0.58
Durand [82] (2008)	26	13 (9.8-15) Median (IQR)	General PICU	0.65
Tran [24] (2007)	44	2.2 – 71.5 (Range)	Cardiac OR	0.74

AUC = Area under the ROC curve; IQR = Inter quarantile range; MAD = Median absolute deviation; N = Number of fluid boluses administered; NR = Non responders; OR = Operating room; R = Responders; SD = Standard deviation.

(ii) Pulse pressure variation (PPV)

Pulse pressure is defined as the difference between the systolic and the diastolic arterial pressure divided by the average of the two, over one respiratory cycle. PPV is calculated using the equation:

$$PPV = \frac{(PP\max - PP\min)}{\frac{1}{2} \times (PP\max + PP\min)} \times 100$$

where

PP max and PP min: maximum and minimum value of the pulse pressure respectively over one mechanical respiratory cycle (fig 2-8).

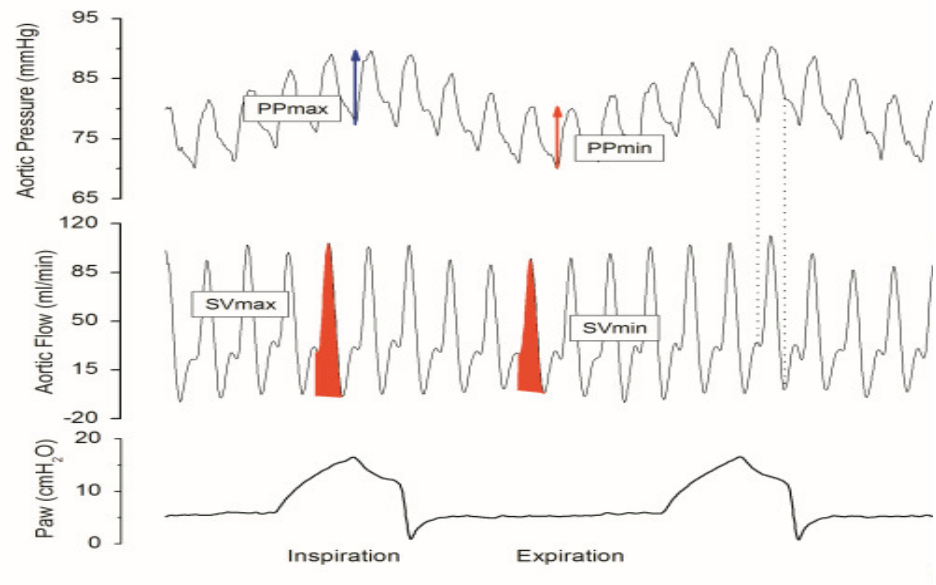

Figure 2-8 Pulse pressure and Stroke volume variation. Note the increase and decrease in pulse pressure and stroke volume during inspiration and expiration during positive pressure ventilation. Reproduced from: Bouchacourt et al. BMC Anesthesiology 2013;13(1):41.[83]

Michard et al proposed the superiority of PPV for prediction of fluid responsiveness over SPV. They suggested that variations in the pulse pressure results not only from the changes in the aortic transmural pressure (mainly related to changes in LV stroke volume) but also from the changes in the extra mural or pleural pressures.[84]

Studies evaluating the use of PPV for fluid responsiveness in adult patients

PPV has been shown to be able to predict fluid responsiveness in different clinical settings (predominantly adult) such as post-coronary artery bypass grafting, perioperative period in patients undergoing coronary artery bypass [85,86] or during major abdominal surgery.[87] A recent systematic review by Yang et al (2014) included twenty-two studies with 807 mechanically ventilated patients with tidal volume more than 8ml/kg, without spontaneous breathing and cardiac arrhythmia. The pooled sensitivity was 0.88 (95% confidence interval (conf. intv.0.81to 0.92) and pooled specificity was 0.89 (95% conf. intv.0.84 to 0.92). A summary receiver operating characteristic curve yielded an area under the curve of 0.94 (95% conf. intv.0.91 to 0.95).[88]

Summary of paediatric studies evaluating the use of PPV for fluid responsiveness

There are only a small number of paediatric studies reporting the utility of PPV for fluid responsiveness. Most were reported after the commencement of this thesis. The range of AUC reported is 0.52 - 0.71 suggesting PPV is unable to predict fluid responsiveness to a high degree. Of note, Renner et al is the only study involving children between the age group 0-2 years who reported the AUC of 0.79 and 0.86 pre and post atrial and /or ventricular septal defect closure. Table 2-6 summarises some of these studies.

Table 2-6 Representative summary of studies evaluating PPV in children

Author (year)	N	Weight (kg)	Setting	AUC
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR Mean (SD)	Neuro OR	0.54
Renner [22] (2012)	26	9.7 (4.3) Mean (SD)	Cardiac OR (Pre op)	0.79
Renner [22] (2012)	26	9.7 (4.3) Mean (SD)	Cardiac OR (Post op)	0.86
de Souza Neto [33] (2011)	19	11(2) Median (MAD)	Neuro OR (0-6 yrs)	0.52
de Souza Neto [33] (2011)	11	32(8) Median (MAD)	Neuro OR (6-14 yrs)	0.60
Durand [82] (2008)	26	13 (9.8-15) Median (IQR)	General PICU	0.59

AUC = Area under the ROC curve; MAD = Median absolute deviation; N = Number of fluid boluses administered; OR = Operating room; SD = Standard deviation.

(iii) Stroke volume variation (SVV)

Stroke volume variation is a result of the distinct variations in the stroke volume of the left ventricle [89] as a result of cardiopulmonary interactions during mechanical ventilation. SVV can be calculated from either Doppler echocardiography[90] or arterial pulse contour based methods.

The maximum and minimum SV values are identified over one respiratory cycle and SVV calculated from the formula mentioned below.

$$SVV = \frac{(SV\max - SV\min)}{\frac{1}{2} \times (SV\max + SV\min)} \times 100$$

where
SV max: maximum stroke volume and
SV min: minimum stroke volume over one mechanical respiratory cycle (fig 2-8).

Pulse contour methods use the same formula as above. The maximum and minimum stroke volumes are estimated over one respiratory cycle using an inbuilt algorithm (which differs according to the commercial monitoring device). The effects of the various factors such as arterial compliance, resistance, impedance is taken into consideration for calculation of the stroke volume.

Biais et al demonstrated an acceptable bias and limits of agreement between SVV measured by pulse contour method and aortic Doppler echocardiography.[91]

Studies evaluating the use of SVV for fluid responsiveness in adult patients

Recently Zhang et al (2011) published a systematic review and meta-analysis regarding the accuracy of SVV in predicting fluid responsiveness in adult subjects.[92] A diagnostic odds ratio of 18.4 for SVV to predict fluid responsiveness at a sensitivity of 0.81 and specificity of 0.80 was reported from 23 studies across all settings. The SVV was of diagnostic value for fluid responsiveness in operating room or intensive care unit patients monitored with the PiCCO or the FloTrac/Vigileo system, and in patients ventilated with tidal volume greater than 8 ml/kg.

However, various authors have reported contradictory results where SVV was found not being able to predict fluid responsiveness accurately. Recently, Biais et al (2012) evaluated the utility of SVV for predicting fluid responsiveness measured by PRAM. Their study included 35 adult patients admitted to a surgical ITU settings. A 12.6% stroke volume variations threshold discriminated between responders and non-responders with a sensitivity of 63% (95% conf. intv.38% to 84%) and a specificity of 69% (95% conf. intv.41% to 89%). The area under the receiver operating characteristic curves was 0.60 (95% confidence interval 0.43-0.76).[93] Similarly, De waal et al [94] and Kee et al [95] reported SVV measured by Flotrac/Vigileo [TM] failed to predict fluid responsiveness in post coronary artery bypass patients. .

In addition, Garcia et al also reported inaccuracy of pulse contour methods for estimation of stroke volume as a result of changing arterial load (arterial compliance, elastance and vascular resistance) due to volume expansion or vasoactive therapy [96] (most patients on advanced haemodynamic monitoring will require such treatment). This will affect the accuracy of SVV estimation and subsequently it's predictive ability for fluid responsiveness.

Studies evaluating the use of SVV for fluid responsiveness in children

A limited number of studies are reported investigating the use of SVV for prediction of response to fluid bolus. Renner et al reported a cut off SVV value of >15% is only able to predict fluid responsiveness with a sensitivity of 60% and specificity of 90% in post-cardiac surgical patients.

The prediction improved after cardiac surgical treatment of closure of ASD and VSD shunts. A summary of the findings is presented in table 2-7.

Table 2-7 Summary of the paediatric studies evaluating SPV for fluid responsiveness

Author (year)	N	Weight (kg)	Setting	AUC
Renner [22] (2012)	26	9.7 (4.3) Mean (SD)	Cardiac OR (Pre op ASD/VSD)	0.70
Renner [22] (2012)	26	9.7 (4.3) Mean (SD)	Cardiac OR (Post op ASD/VSD)	0.78
Tran [24] (2007)	44	2.2 – 71.5 (Range)	Cardiac OR	0.74

AUC = Area under the ROC curve; ASD = Atrial septal defect; N = Number of fluid boluses administered; OR = Operating room; SD = Standard deviation; VSD = Ventricular septal defect.

(iv) Doppler measured dynamic markers

(a) Changes in aortic blood flow peak velocity measured by trans-thoracic Doppler (ΔVpeakAo)

Changes in the aortic blood flow peak velocity (ΔVpeakAo) can be measured using the Doppler technique (explained in chapter 1) with either transthoracic or transoesophageal approach. ΔVpeakAo is a result of cardiorespiratory interactions during mechanical ventilation (as for other dynamic markers).

Pulsed Doppler aortic blood flow velocity estimation at the exact level of the annulus from the apical five-chamber view over one mechanical respiratory cycle provides an estimation of maximal and minimal values of aortic peak velocity (VpeakAo). (see fig 2-9).

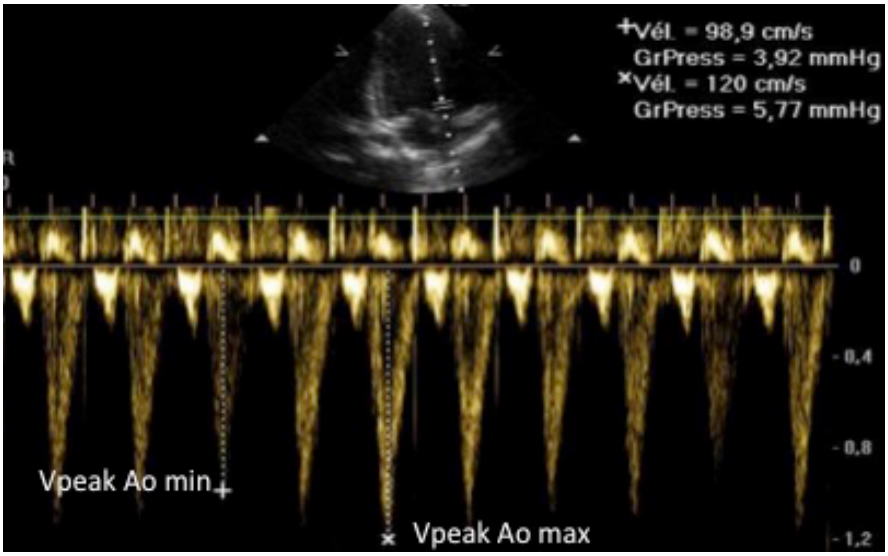

Figure 2-9 Measurement of Vpeak Ao maximum and minimum over one respiratory cycle using trans thoracic doppler. Reproduced from: Durand P et al. Intensive Care Med 2008;34:888–94.[82]

Changes in the blood peak velocity over one respiratory cycle is calculated as follows [97]

$$\Delta VpeakAo\ (\%) = \frac{(VpeakAo\max - VpeakAo\min)}{\frac{1}{2} \times (VpeakAo\max + VpeakAo\min)} \times 100$$

where

ΔVpeakAo: change in the aortic blood flow peak velocity

VpeakAo max and VpeakAo min are the maximum and minimum aortic blood flow velocity over one mechanical respiratory cycle.

Limitations unique to measurement of ΔVpeakAo

Measurement of ΔVpeakAo requires the use of pulsed Doppler directed at the aortic valve annulus level. This requires appropriate probe position and special operator dependent skills, making it prone to operator related errors. Belloni et al demonstrated this particular error in their study involving 19 patients. They reported inability of ΔVpeakAo measured by transoesophageal Doppler to predict fluid responsiveness with possible explanation of high level of operator dependence for measurement of this parameter.[98] Operator dependence is less during transoesophageal Doppler measurement of ΔVpeakAo in the descending aorta.

Studies evaluating the use of ΔVAo for prediction of fluid responsiveness in children

Various authors have evaluated its use for fluid prediction in children; most have reported encouraging results.

Durand et al studied the effects of volume expansion in 26 mechanically ventilated children. Increase in stroke volume greater than 15% was regarded as a positive response to fluid bolus administration. They demonstrated ΔVpeakAo in responders was higher than that in non-responders [19% (12.1–26.3) vs. 9% (7.3–11.8), p = 0.001]. ΔVpeakAo was able to predict fluid responsiveness with area under ROC curve of 0.85 (95% conf. intv.0.99–1.8), p = 0.001]. The best cut-off for ΔVpeakAo reported was 12%, with sensitivity, specificity and positive and negative predictive values of 81.2%, 85.7%, 93% and 66.6%, respectively. They also reported a positive linear correlation between baseline ΔVpeakAo and change in stroke volume following volume expansion (Rho = 0.68, p 0.0012). [82]

Choi et al also demonstrated similar results in their study involving fluid bolus administration in 21 mechanically ventilated post ventricular septal defect repair children. They also showed baseline ΔVpeakAo to be higher in the responders than non- responders (23.1 ± 5.7% vs. 14.0 ± 7.7%; p = 0.006) . ΔVpeakAo was able to predict fluid responsiveness as shown by a receiver operating characteristic curve area of 0.83 (95% conf. intv. 0.61–1.00; p = 0.01) . However, they defined the cut off value of ΔVpeakAo of 20% with a sensitivity of 91% and specificity of 90%.[23]

A summary of the studies evaluating its use in children is presented in table 2-8.

Table 2-8 Summary of the studies evaluating the use of respiratory variation in blood peak flow velocity in aorta in children

Author (year)	N	Weight (kg)	Doppler	Setting	AUC
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR Mean (SD)	TTE	Neuro OR	0.80
de Souza Neto [33] (2011)	19	11(2) Median (MAD)	TTE	Neuro OR (0-6 yrs)	1.00
de Souza Neto [33] (2011)	11	32(8) Median (MAD)	TTE	Neuro OR (6-14 yrs)	1.00
Renner [100] (2011)	27	10.4(6.3) Mean (SD)	TOE	Cardiac OR	0.92
Choi [23] (2010)	21	12(4) R, NR Mean (SD)	TTE	Cardiac PICU	0.83
Durand [82] (2008)	26	13 (9.8-15) Median (IQR)	TTE	General PICU	0.85

AUC = Area under the ROC curve; ASD = Atrial septal defect; MAD = Median absolute deviation; N = Number of fluid boluses administered; NR = Non responders; OR = Operating room; R = Responders; SD = Standard deviation; TTE = Transthoracic echocardiography defect; TOE = Transoesophageal echocardiography.

(b) Change in velocity time integral (ΔVTI) or stroke distance

Doppler velocity time integral (VTI) of left ventricular outflow tract, also known as stroke distance, is measured using the transoesophageal or transthoracic approach with commercially available Doppler probes (figure 2-10).

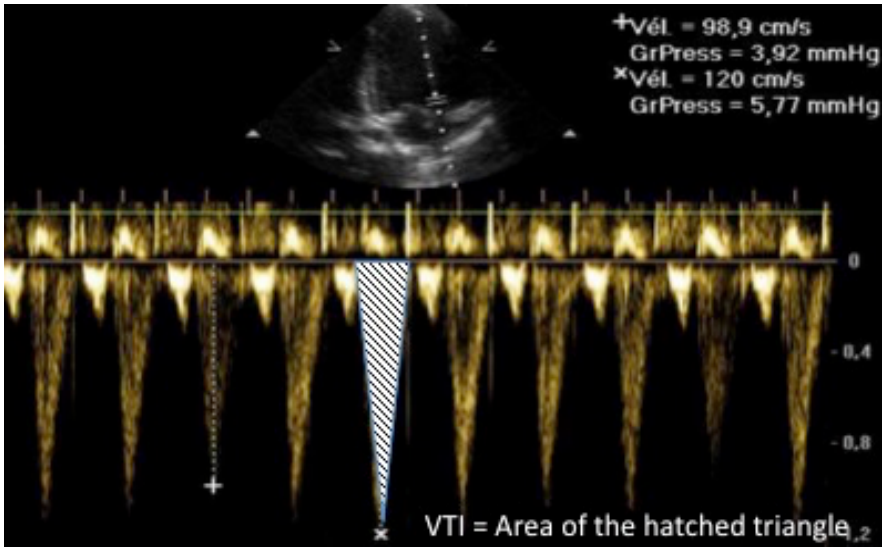

Figure 2-10 Calculation of VTI from spectral representation of Doppler of the aortic blood flow. VTI equals the area of the hatched triangle. Reproduced from: Durand P et al. Intensive Care Med 2008;34:888–94.[82]

The maximum and minimum VTI are recorded over one mechanical respiratory cycle. ΔVTI is calculated from the following formula:

$$\Delta VTI(\%) = \frac{(VT\,\mathrm{Im}\,ax - VT\,\mathrm{Im}\,in)}{\frac{1}{2} \times (VT\,\mathrm{Im}\,ax + VT\,\mathrm{Im}\,in)} \times 100$$

where

ΔVTI: change in the Doppler VTI of the blood in left ventricular outflow tract

VTI max and VTI min: maximum and minimum Doppler VTI of blood in left ventricular outflow tract.

Limitations or Sources of errors for measurement of ΔVTI

These are similar to any other method utilising Doppler based estimations such as positioning and fixation of probe to ensure the angle of insonation between the Doppler beam and direction of blood flow is less than 15° (see chapter 1, page 46). This predisposes this technique particularly vulnerable to operator related errors.

Paediatric study investigating the use of ΔVTI for prediction of fluid responsiveness

Renner and colleagues have shown encouraging results in their study involving 27 pre cardiac surgical, anaesthetised and mechanically ventilated children. The AUC was 0.84 with an optimal threshold value ≥ 4% (sensitivity 84% and specificity 71%) (table 2-9).

Table 2-9 Summary of study evaluating the role of VTI for prediction of fluid responsiveness in children

Author (year)	N	Weight (kg)	Doppler	Setting	AUC
Renner [99] (2011)	27	10.4(6.3) Mean (SD)	TOE	Cardiac OR	0.84

AUC = Area under the ROC curve; N = Number of fluid boluses administered; OR = Operating room; SD = Standard deviation; TOE = Transoesophageal echocardiography.

(v) Change in pulse oximetry plethysmography (ΔPOP) and pulse variability index (PVI)

The comparison of absorbencies at different wavelengths (660 nm and 940 nm) allows estimation of the relative concentrations of oxyhaemoglobin and haemoglobin (i.e. saturation) by pulse oximetry. This is a continuous monitoring system generating a plethysmographic waveform (see fig 2-11).

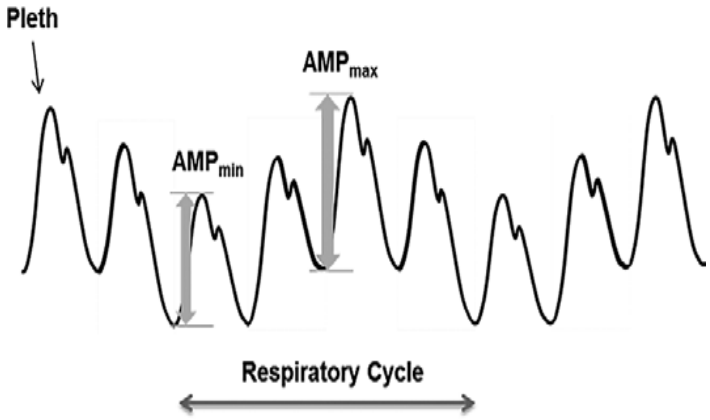

Figure 2-11 Plethysmography waveform representing maximum and minimum amplitudes over one respiratory cycle.Reproduced from: Addison P. Anesth Analg 2014;119:1293–1306.[100]

ΔPOP is extracted from the same waveform as suggested by Cannesson et al.[101] They defined ΔPOP as the respiratory variation in pulse oximetry plethysmographic (POP) waveform amplitude:

$$\Delta POP = \frac{AMP\max - AMP\min}{\frac{1}{2} \times (AMP\max + AMP\min)} \times 100$$

where
AMPmax and AMPmin: maximum and minimum amplitude of pulse waveform of plethysmography signal over a respiratory cycle respectively.

ΔPOP is based upon similar principles as PPV and many authors have reported a good correlation between ΔPOP and PPV in adult patients.[102,103]

Perfusion variability index PVI (Masimo Corp., Irvine, CA) is a proprietary algorithm for automated and continuous representation of the respiratory variations in the plethysmographic waveform amplitude, using perfusion index (PI) as a surrogate. Perfusion index is an assessment of the pulsatile strength at a specific monitoring site (such as hand, finger or foot). It is calculated with pulse oximetry by expressing the pulsatile signal (during arterial inflow) as a percentage of the non-pulsatile signal, both of which are derived from the amount of infrared (940 nm) light absorbed.[104]

PVI is the maximum change in the perfusion index (PI) over a time interval incorporating at least one complete respiratory cycle. This is represented by the equation below:

$$PVI = \frac{(P\mathrm{Im}ax - P\mathrm{Im}in)}{P\mathrm{Im}ax} \times 100$$

where
PI*max* and PI*min* are the maximum and minimum perfusion index over one respiratory cycle.

Limitations specific for the measurement of ΔPOP and PVI

Since both ΔPOP and PVI are dynamic markers, they are subject to similar disadvantages or sources of error as other dynamic markers. In addition, the variability of results is compounded by the procedure for calculating ΔPOP differs across various studies in terms of averaging period and location of signal interrogation.[100]

Adult studies evaluating the use of ΔPOP and PVI for prediction of fluid responsiveness

Δ POP and PVI have been directly compared with each other and found to be comparable in performance for prediction of fluid responsiveness or correlation with PPV.[105,106] In addition, systematic reviews of the literature undertaken by Antonsen and Kirkebøen [107] and Sandroni et al concluded that ΔPOP and PVI were equally effective in predicting fluid responsiveness in ventilated adult patients in sinus rhythm.[108]

Paediatric studies evaluating the use of ΔPOP and PVI for prediction of fluid responsiveness

ΔPOP was unable to predict fluid responsiveness in children in studies conducted by Chandler et al [109] de Souza Neto et al [33]. Results for utility of PVI in children are variable with some authors reporting it to be useful [21, 99] while others did not find it accurate enough.[33,109]

Byon et al demonstrated PVI was able to predict for fluid responsiveness in their study involving thirty-three mechanically ventilated children undergoing neurosurgery, a PVI value of 11% predicted fluid responsiveness with a sensitivity of 73.3% and a specificity of 86.7%. The area under the curve was 0.767 (95% conf. intv.0.597 – 0.936).[21]

On the contrary, de Souza et al in their study involving thirty mechanically ventilated children reported an area under the curve for ΔPOP and PVI to be 0.51 and 0.63 respectively in 0-6 year old and 0.57 and 0.54 in 6-14 year olds.[33]

A summary of paediatric studies is presented in table 2-10 on the next page.

Table 2-10 Summary representing paediatric studies investigating the utility of POP and PVI

Author (year)	N	Weight (kg)	Setting	AUC
ΔPOP				
Chandler [109] (2011)	19	26.3 (Median)	Cardiac cath	0.56
de Souza Neto [33] (2011)	19	11(2) Median (MAD)	Neuro OR (0-6 yrs)	0.51
de Souza Neto [33] (2011)	11	32(8) Median (MAD)	Neuro OR (6-14 yrs)	0.57
PVI				
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR Mean (SD)	Neuro OR	0.77
Chandler [109] (2011	19	26.3 (Median)	Cardiac cath	0.54
de Souza Neto [33] (2011)	19	11(2) Median (MAD)	Neuro OR (0-6 yrs)	0.63
de Souza Neto [33] (2011)	11	32(8) Median (MAD)	Neuro OR (6-14 yrs)	0.54
Renner [99] (2011)	27	10.4(6.3) Mean (SD)	Cardiac OR	0.78

AUC = Area under the ROC curve; MAD = Median absolute deviation; N = Number of fluid boluses administered; N = Non Responders; OR = Operating room;; ΔPOP = Change in pulse oximetry plethysmography; R = Responders, PVI = Perfusion variability index; SD = Standard deviation.

2.2.4 General sources of error or limitations of dynamic markers

Dynamic markers have certain limitations or sources of error, which should be taken into consideration while interpreting them in clinical practice.[110]

(i) Arterial pressure measurement system: The arterial pressure curves are obtained from fluid filled catheter systems. Several factors, such as kinking or clot formation, and excessive tubing length can affect the quality of signal, thus affecting the accuracy of the measurements.

(ii) Dysarrythmia: Arrythmias will affect the beat-to-beat variability of stroke volume hence interfering with estimation of these markers to a variable degree. This is particularly true for atrial fibrillation or extra systoles.

Measurement by PRAM depends upon the identification of dicrotic notch on the arterial pressure waveform. This identification may be difficult in cases of arrythmias leading to inaccurate measurements.

(iii) Dynamic markers have limited value in assessing fluid responsiveness in settings where the pleural pressure changes are small during the respiratory cycle. This may be seen during spontaneous breathing and open chest conditions [111,112] common after neonatal cardiac surgery. De Backer et al demonstrated PPV to be a reliable indicator for fluid responsiveness only when the tidal volume is greater than 8ml/kg.[113] Similar observations have been reported by various other authors.[114-116]

iv) High ventilator rates or high frequency oscillation: Higher mechanical ventilatory rates (not uncommon in small children) decreases the ratio of heart rate to respiratory rate. The number of cardiac cycles per respiratory cycle may be too low to allow variations in stroke volume.[117]

(v) Right ventricular failure: PPV and SVV may not be reliable indicators for preload dependence in case of right ventricular failure. This is because the major contribution is by an inspiratory increase in afterload as opposed to decrease in preload. In this context the lack of

response to fluid administration with high PPV or SVV should be indicative of right ventricular failure.[118]

(vi) Influence of vasoconstrictors on the dynamic variables: Vasoconstrictors influence arterial load as a result of predominant effect on effect on arterial compliance, elastance and vascular resistance. This can lead to inaccurate estimation of stroke volume (hence affecting accuracy of estimation of SVV, SPV and PPV).

Garcia et al studied the accuracy of eight different pulse contour algorithms during acute changes in arterial load induced by vasoactive (norepinephrine infusion) or volume expansion therapy. Three different aspects of arterial load were evaluated- total systemic vascular resistance, arterial compliance and arterial elastance while comparing CO estimation between oesophageal Doppler and different (eight) pulse contour algorithms. The range of percentage error for cardiac output measurements was reported between 27%(best performing algorithm) to 49.8% (worst performing algorithm) during vasoconstrictor therapy . Further, the mean bias, limits of agreement and percentage error were significantly higher in the vasoconstrictor group as compared to volume expansion group. This was a result of more pronounced and statistically significant changes in arterial load (especially arterial compliance and elastance) in the vasoconstrictor group as compared to fluid administration.[96]

Nouira et al demonstrated a significant decrease in PPV and SPV following norepinephrine infusion during haemorrhage in animal study [119]. Renner and colleagues also reported similar findings in their study with the use of norepinephrine in their porcine haemorrhagic model [120]. However, Hadian et al demonstrated (n=15 cardiac patients) that PPV (and SVV) decreased after volume loading and increased after initiation of vasodilators but there was no effect on PPV (or SVV) after increase of inotropes or vasoconstrictors. In summary, additional larger trials are required to clarify the effect of vasoconstrictors in hypovolaemic patients on dynamic variables.[121]

(vii) Influence of intra-abdominal hypertension (IAH) on dynamic variables: Raised abdominal pressures can lead to impaired venous return as a result of IVC obstruction. This may have a

direct effect on the measurement of dynamic indices. Duperett et al reported increase in SPV, PPV and IVC flow associated with increasing intra-abdominal pressures especially in the presence of hypovolaemia.[122] This may be partly attributed to the associated changes in the pleural pressures. Renner et al also demonstrated failure of SVV to predict preload dependence during IAH in their porcine model. However, PPV remained sensitive and specific during IAH to predict fluid responsiveness. Interestingly, the threshold value for PPV almost doubled to do so.[123]

2.4 Other tests for prediction of SV response to fluid bolus administration

(i) Passive leg raising (PLR) induced changes in cardiac output

Passive leg raising manoeuvre transfers blood from the venous compartment of legs and abdomen to the intra-thoracic compartment. This leads to an increase in preload of the right and subsequently left ventricle.[124,125] The haemodynamic changes induced are not sustained (due to compensatory mechanisms of the body) and are reversible once the legs are returned to supine position.[126] The effect of PLR on cardiac output in responders occurs within thirty seconds to one minute.[126]

The advantages of performing PLR are:

(i) Relatively simple procedure to perform,
(ii) The effects are quick and reversible and
(iii) PLR does not lead to additional volume overload in non-responders.
(iv) PLR is shown to be accurate in self-ventilated patients and in the settings of arrhythmias.
The last two characteristics differentiate PLR from other dynamic markers of fluid responsiveness.

The limitations of PLR testing are:

(i) PLR testing is not feasible where patient mobility is limited or not allowed such as severe trauma or head injury patients.[127]

(ii) PLR represents an inconsistent quasi fluid challenge in children, as the proportionate blood volume in the legs alters across paediatric age and weight range. This leads to difficulties in standardisation and interpretation of the test. This is most likely related to somatic growth and changes in body segment proportions with increasing age during childhood.

Adult studies evaluating the use of PLR for the prediction of fluid responsiveness

Cavallaro and colleagues performed a systematic review on the diagnostic accuracy of PLR for prediction of fluid responsiveness in adult patients. A total of 353 patients from nine studies were included into the study. The pooled sensitivity and specificity of PLR induced change in CO for predicting fluid responsiveness were 89.4% (conf. intv.84.1-93.4%) and 91.4% (conf. intv.85.9-95.2%) respectively. The pooled area under the receiver operating characteristics curve (AUC) was 0.95 (0.92-0.97). The threshold for prediction of fluid responsiveness varied between 8 and 15%. The pooled correlation coefficient between the baseline value of PLR induced changes in CO and corresponding increase in CO after volume expansion was 0.81 (0.75-0.86). The pooled difference in mean PLR induced change in CO values between responders and non-responders was 17.7% (13.6-21.8%, $p < .0001$). No significant differences were identified (a) between ventilated and spontaneously breathing patients (b) between patients in sinus rhythm versus and arrhythmias.[128]

Paediatric study evaluating the use of PLR for the prediction of fluid responsiveness

The only paediatric study evaluating PLR for prediction of fluid responsiveness is by Lukito V et al. They studied the role of PLR in predicting fluid responsiveness in forty children admitted to intensive care unit. They reported a significant relation between changes in cardiac index to predict fluid responsiveness ($p = .012$, $r(2) = .22$, 95% confidence interval 1.529 to 31.37). A cardiac index increase by ≥10% induced by passive leg raising predicted preload-dependent status with sensitivity of 55% and specificity of 85% (area under the curve 0.71 ± 0.084, 95% Conf. intv. 0.546-0.874). The authors concluded that the concomitant measurements in cardiac index changes after the passive leg raising manoeuvre can be helpful in predicting fluid responsiveness with subsequent fluid resuscitation.[129]

(ii) Change in Inferior vena cava diameter (ΔIVC dia)

The inferior vena cava (IVC) is an intra-abdominal compliant blood vessel returning blood from the lower parts of the body to the heart. It accounts for approximately 75% of venous return to the right side of the heart in adults, but less in children.[130] It acts as a reservoir of blood and is subjected to abdominal pressure. The calibre of IVC is altered by phases of respiration [131], blood volume [132] and right heart function.[133]

Takata et al suggested that the IVC diameter depends on the extra-mural IVC pressure i.e right atrial pressure and the abdominal pressure.[134] During spontaneous ventilation, cyclic changes in pleural pressure transmitted to the right atrium produces inspiratory decrease in IVC diameter leading to cyclical changes in venous return.[135] This cyclical change in vena cava diameter is most significant during hypovolaemia and is attenuated when the vessel is dilated. Kircher et al demonstrated that the inspiratory decrease in the IVC diameter was well correlated with the right atrial pressure during spontaneous breathing.[136]

On the contrary, IVC diameter increases to a maximum at inspiration during positive pressure ventilation. Positive pressure inspiration leads to an increase in the pleural pressure which in turn rises the intravascular pressure of the right atrium. This will decrease the venous return gradient leading to dilatation of the IVC.[137] This inspiratory dilatation is even greater during high compliance states such as hypovolaemia.[138]

The IVC diameter is visualised by a sub-coastal view in a longitudinal section with the use of trans thoracic echocardiography. The diameter is measured in M-mode coupled to the two dimensional mode either just upstream of the origin of supra hepatic veins [137] or just below (3cm) the junction of IVC to right atrium.[139] Both inspiratory and expiratory diameters are measured over a single respiratory cycle.

Limitations specific to the measurement of ΔIVC dia

Measurement of ΔIVC dia requires the use of specific skills related to echocardiography making it prone to errors.

Paediatric studies evaluating the use of ΔIVC dia for the prediction of fluid responsiveness

Choi et al investigated the effect of fluid bolus administration (10ml/kg) in 21 post ventricular septal defect repair children in their intensive care unit. They demonstrated Δ IVC dia was higher in the responders (increase in SV >15%) as compared to the non-responders (26.5 ± 16.2% vs. 9.2 ± 9.1%; p = 0.008). The AUC was 0.85 (95% Conf. intv., 0.69-1.00; p = 0.01).[23]

However, on the contrary, Byon et al did not find Δ IVC dia to be a useful marker for prediction for fluid responsiveness. They studied thirty-three mechanically ventilated children undergoing neurosurgery. There was no difference in Δ IVC dia between responders and non-responders [21].

A summary of these studies evaluating its use in children is presented in table 2-11.

Table 2-11 Summary of the two studies evaluating the role of Δ IVC diameter for predicting fluid responsiveness in paediatric setting

Author (year)	N	Weight (kg) Mean (SD)	Doppler	Setting	AUC
Byon [21] (2013)	33	24.3(10.2) R 23(9.2) NR	TTE	Neuro OR	0.37
Choi [23] (2010)	21	12(4) R, NR	TTE	Cardiac PICU	0.85

AUC = Area under the ROC curve;; N = Number of fluid boluses administered; NR = Non responders; OR = Operating room; R = Responders; SD = Standard deviation; TTE = Transthoracic echocardiography; TOE =Transoesophageal echocardiography.

(iii) End expiratory occlusion test

Inspiration with positive pressure mechanical ventilation reduces right ventricular preload. Pause in the mechanical insufflation at end expiration for 10-15 seconds suppresses this reduction in preload and may lead to increase in the cardiac preload to an extent to be used for prediction of fluid responsiveness for subsequent volume expansion.[140] Two major advantages of this test are (i) can be used in patients with arrhythmias and (ii) patients do not need to be paralysed.

Various authors have reported conflicting results about the use of this test in adult patient group .[141,142] There are no paediatric studies reported in the literature evaluating the use of this test for prediction of fluid responsiveness.

2.5 Arterial dP/dt_{max} as a marker of left ventricular contractility

Dynamic or static markers, irrespective of their ability to predict response to fluid bolus administration, are unable to provide any meaningful information regarding underlying myocardial contractility - a major determinant in cardiac output.

The contribution of myocardial contractility towards the response for fluid bolus administration is increasingly been recognized. The slope between the change in preload and stroke volume on the Frank-Starling curve is partly dependent upon the contractile state of myocardium (see fig 2-1). Disease processes like septic shock has a far greater effect on ventricular contractility than was previously recognised [143]. Hence, an accurate estimation of left ventricular contractility is important in order to improve the prediction of response to fluid bolus administration.

The gold standard for estimation of left ventricular contractility is the end systolic pressure volume relationship. The slope of this relationship is referred to as end systolic elastance. providing an index of left ventricular contractility.[144,145] However, estimation of end systolic elastance is an invasive procedure involving left ventricular catheterization. This is a fairly high-risk procedure in the critically ill paediatric population due to the small, variable size and associated haemodynamic compromise. A non-invasive or minimally invasive technique for estimation of the left ventricular contractility will be more appropriate and practically useful. A number of novel non-invasive [146] or invasive markers have been studied such as peak first and second time derivative of ventricular pressure, peak isovolaemic power, peak aortic blood acceleration, peak fibre velocity, mean aortic blood flow, time-tension index. Most of them failed to provide any valid or relevant estimation of the left ventricular contractility.[147]

Peak first derivative of left ventricle pressure (LV dP/dt_{max}) provides a reliable estimate of the myocardial contractility.[148,149] However, its estimation will require invasive catheterization in the left ventricle with all the perils as discussed above.

Most of the critically ill patients exhibiting cardiovascular instability have arterial lines in situ. Arterial dP/dt_{max} is related to LV dP/dt_{max}, and can be estimated from the pressure waveform

from these catheters. This is the maximum ascending slope of the arterial pressure waveform (fig 2-12).

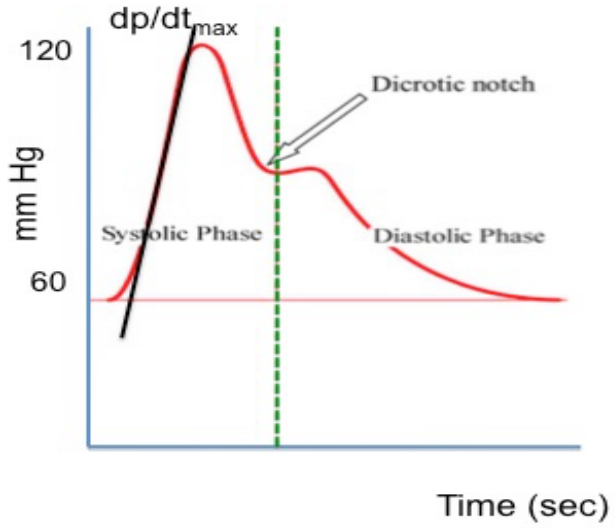

Figure 2-12 Estimation of dP/dt max from arterial waveform. This is the maximum ascending slope of the arterial pressure waveform.

De Hert et al compared dP/dt_{max} estimated from a femoral artery pressure tracing to left ventricular (LV) dP/dt_{max} during various alterations in myocardial loading and contractile function in seventy adult patients scheduled for coronary artery bypass surgery. They demonstrated LV and femoral dP/dt_{max} were significantly correlated ($r = 0.82$, $p < 0.001$), but femoral dP/dt_{max} systematically underestimated LV dP/dt_{max} (bias = -361 +/- 96 mmHg/s)]. A very close linear relationship ($r = 0.93$) and a good agreement (bias = -5 +/- 17 mmHg/s) were found between the changes in femoral dP/dt_{max} and LV dP/dt_{max}. This relationship persisted during different interventions (leg raising, calcium administration, and dobutamine infusion).[150]

Similarly Scolletta and colleagues compared LV dP/dt_{max} measured from echocardiography to peripheral arterial dP/dt_{max} measured by PRAM in seventy critically ill adult patients. They reported a strong linear correlation between the two ($r=0.93$, $p<.001$). The mean bias between the two was 23.7 mmHg/s (95 % CI -23.6 to 71.0) with limits of agreement of -372 to +383

mmHg/s (lower 95 % CI -454 to -290; upper 95 % CI 338 to 502) and a relative percentage error of 28% .[151]

On the other hand, Sharman et al in their study in adult males concluded radial pressure waveform dP/dt max to be a poor reflection of left ventricular systolic function measured by high fidelity catheter system and echocardiography. They demonstrated a poor, but statistically significant, correlation between the LV dP/dt_{max} measured using catheter and estimated via radial artery dP/dt_{max} (R^2=0.006; P < 0.05) during rest and exercise.Similar weak to non-significant association was demonstrated between radial dP/dt_{max} and all echocardiographic measures analogous to LV dP/dt_{max} at rest or peak dobutamine induced stress (R^2= -0.12; P = 0.01).[152]

Paediatric studies investigating the role of peripherally estimated dP/dtmax for estimation of left ventricular contractility

Unlike adult studies, it has been suggested that children demonstrate a stronger relationship between LV and arterial dP/dt_{max}. Masutani et al evaluated the role of Aortic dP/dt_{max} for estimation of LV contractility in 75 children (30 control; 45 disease). They demonstrated a high correlation between the measured LV dP/dt_{max} and the estimated LV dP/dt_{max} (from aortic LV dP/dt_{max}) in both control group and in children with cardiac diseases under variable contractility states (dobutamine infusion) and heart rate (atrial pacing) [r=0.89, p<.0001]. They concluded that LV dP/dt_{max} is closely correlated and can be reasonably estimated from aortic dP/dt_{max} . This was based upon their results that the relationship between aortic dP/dt_{max} and vascular mechanical and loading properties (such as impedance and mean arterial pressure) was maintained irrespective of the underlying cardiac condition or cardiovascular state.[153]

Kawasaki et al studied 31 children with cardiovascular diseases for estimation of LV dP/dt_{max} from the maximum rate of pressure rise in peripheral arteries (brachial and radial arteries).

Their group also demonstrated that the estimated LV dP/dt_{max} correlated well with the measured LV dP/dt_{max} ($r=0.91$, $p<.0001$). This high correlation between the two persisted even after changes in contractility were made using dobutamine infusion in randomly selected patient subgroup.[154]

A gap regarding the utility and validity of this marker in paediatric population is well recognised. Our study investigated the role of dP/dt_{max} (measured by PRAM) as a marker of myocardial contractility in determining the response to fluid bolus administration in a cohort of critically ill children. We did not aim to validate this marker in our study.

2.6 Summary

This chapter summarized (a) the common dynamic and static markers used in clinical practice for discrimination between responders and non-responders to fluid bolus administration (b) the role of dP/dt max for estimation of ventricular contractility.

Review of the literature pointed towards dynamic markers outperforming static markers. Change in aortic blood flow peak velocity and passive leg raising induced changes in cardiac output showed consistent results in their accuracy. However, the role of these markers is only well studied in adult patient group and further studies investigating their role in children in different clinical settings are still required.

In addition to the preload and afterload, response to fluid bolus administration is also governed by state of myocardial contractility. An accurate assessment of this factor is equally important to prevent fluid overload in critically ill patients.

Finally, it must be remembered that fluid responsiveness in itself does not mean that the patient requires fluid resuscitation. Most of the healthy persons are fluid responsive but do not require fluid bolus administration. The decision regarding fluid requirement or augmentation of CO

should be based on the overall clinical and biochemical picture in addition to these markers of fluid responsiveness.

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Chapter 3 Description of Transpulmonary Ultrasound Dilution (TPUD) and Pressure Recording Analytical Method (PRAM)

3.1 Transpulmonary ultrasound dilution technique (CO Status^{TM}, NY, USA)

Transpulmonary ultrasound dilution (TPUD) is an indicator dilution based technique utilising normal saline as the indicator. It incorporates an extra-corporeal arterio-venous (AV) loop and two reusable ultrasound sensors - one attached to each end of the AV loop (fig 3-1). The AV loop is primed with heparin saline and the two ends are connected to the pre-existing arterial and central venous catheters. A roller pump provides a constant flow of blood at a rate of 6-12 ml/min in the AV loop during the measurement. Isotonic saline (0.5 - 1 ml/kg, maximum 30ml) is used as an indicator. The speed of the injection will depend upon the size of the venous catheter and the volume of saline injected. The venous sensor directly measures the injection volume. This improves accuracy by eliminating operator dependence.

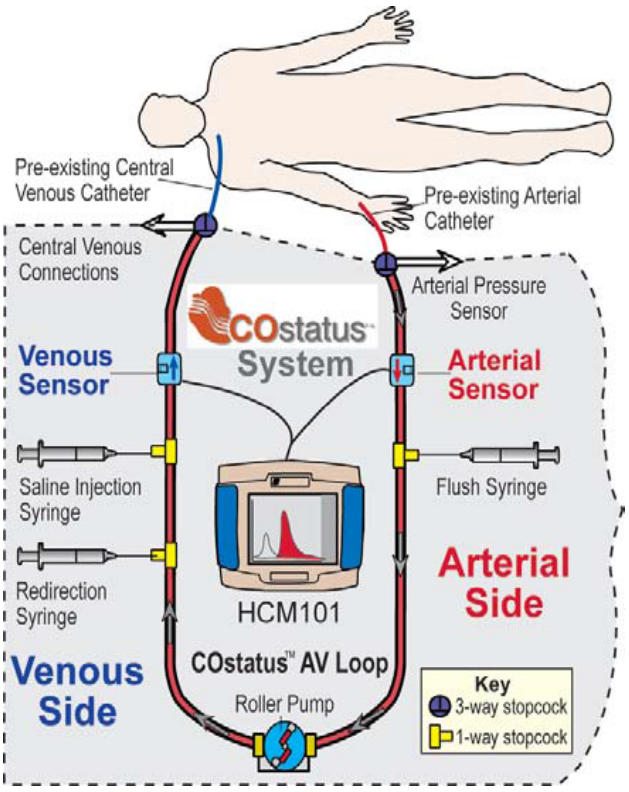

Figure 3-1 TPUD set up with AV loop (with permission form Transonic, NY, USA).

The velocity of an ultrasound beam directed through a column of isotonic saline at body temperature is 1533 m/sec. This is different from that through the blood (ranging between 1570 – 1585 m/sec). Thus, saline injected into the venous limb will produce a transient change in the ultrasound velocity in both the venous and arterial limbs, in proportion to the degree of dilution. Figure 3-2 shows a screen shot from TPUD monitor after a normal saline injection. The venous curve (marked as 'a' in fig 3-2) is generated as a result of the saline injection by the venous sensor. It only represents the shape (or quality) of the injection and is not normalised to percentage dilution on the 'y' axis. The arterial dilution curve (marked 'b' in fig.3-2) is generated by the arterial sensor as a result of a transient change in the ultrasound blood velocity following the saline injection. It is expressed graphically on the monitor with the 'y' axis representing percentage of saline concentration in the arterial blood and the 'x' axis being time. It is worth noting that the venous curve will be much bigger in size than the arterial curve if similar scaling is used for both the curves on the y axis.

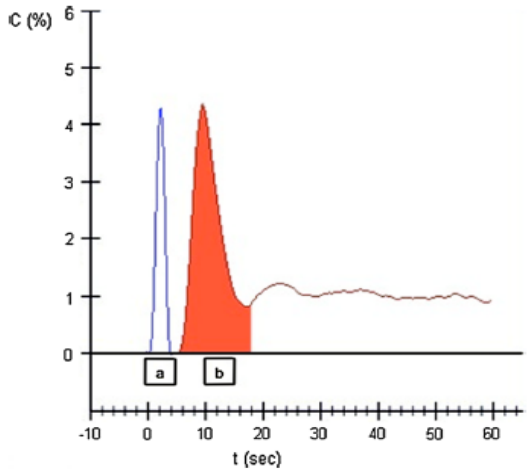

Figure 3-2 Display from TPUD monitor. Dilution curve of a normal four chamber heart. The 'Y' axis, C%, represents the percentage concentration of saline in the arterial blood; the 'X' axis is time (seconds). The dilution curve marked 'a' is generated from the ultrasound sensor on the venous limb at time of injection, while the dilution curve 'b' represents saline dilution of arterial blood. The latter is used to calculate cardiac output. Reproduced with permission form Transonic, NY, USA

The quality of both the curves is inspected to ensure accuracy of the technique. Figure 3-3 demonstrates examples of abnormal graphs that are rejected and measurements are repeated

till an accurate reading is obtained. The graph on the left (marked with blue arrow) shows an abnormal venous injection and the one on the right (marked with red arrow) shows an abnormal dilution curve.

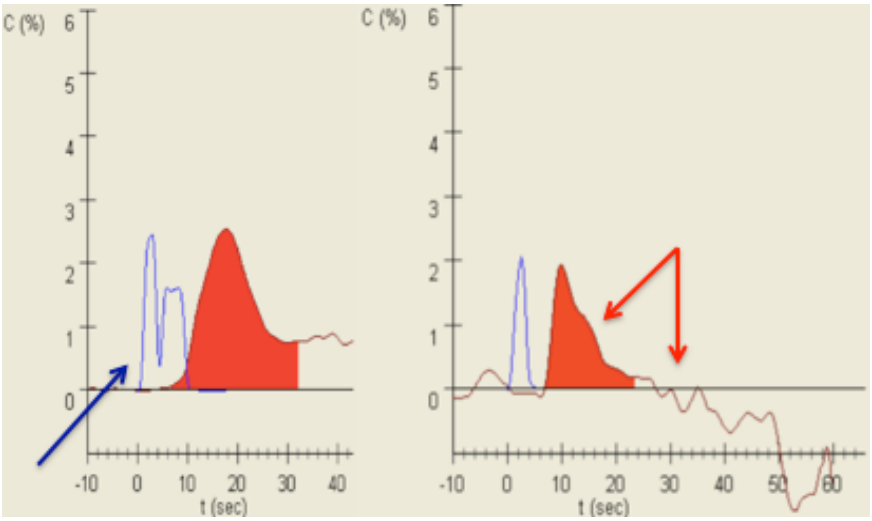

Figure 3-3 Abnormal venous injection and arterial dilution curves. The blue arrow points towards humped (abnormal) venous injection curve. Normally, it should be a smooth narrow curve. Red arrows point towards an abnormal downslope part of the indicator dilution curve probably due to abnormal signal noise. Reproduced with permission form Transonic, NY, USA.

The software calculates the haemodynamic variables and displayed on the monitor. A set comprising of two or three measurements is taken to counteract the variations of CO in different respiratory phases and the readings averaged. The AV loop is flushed with the heparinized saline and is left in situ for the next set of measurements. In addition to measuring CO, TPUD also gives a qualitative and quantitative estimation of anatomical shunts and three novel markers of preload estimation as described below.

3.1.1 Measurement of cardiac output

TPUD generates an arterial dilution curve based upon changes in the ultrasound velocity in the blood after a saline injection as explained above. Cardiac output is calculated using the Stewart-Hamilton equation.[1]

$$CO = \frac{(UV_{blood} - UV_{saline}) \times V_{inj}}{\int UVa(t)\,dt} = \frac{V_{inj}}{\int Ca(t)(dt)} = \frac{Volume\ of\ indicator\ injected}{Area\ under\ the\ dilution\ curve}$$

where

V_{inj} : volume of injected saline quantified by the venous sensor

(UV_{blood} – UV_{saline}): difference between the ultrasound velocity of blood and saline measured by the venous sensor

UV_a: refers to the changes in the arterial blood ultrasound velocity measured by the arterial sensor

$\int Ca(t)\,(dt)$ is the area under the dilution curve of the saline concentration of the injected saline in the arterial blood calculated from the changes in blood ultrasound velocity and the difference between the ultrasound velocity of blood and saline (measured by the venous sensor). This assumes a linear relationship between the changes in blood ultrasound velocity and saline dilution.

The theory and in-vitro validation of this technique is reported in detail by Krivitsky et al.[2]

TPUD has been validated for measurement of CO in paediatric animal model [3] and children with reference to other standard methods such as thermodilution [4], Fick method [5] and flow probes.[6]

Crittendon 3rd et al compared TPUD with pulmonary artery thermodilution in twenty-eight patients with a median age and weight of 8 years and 31 kg respectively. The mean thermodilution cardiac index was 3.02 l/min/m^2 (IQR 2.14 - 4.54l/min/ m^2) against the mean cardiac index measured by TPUD of 3.05 l/min/m^2 (IQR 2.81-3.45l/min/m^2). Bland-Altman analysis revealed good clinical agreement with a mean bias of -0.004 l/min with a precision of 0.8 l/min/m^2 at 2 SD. The percentage error of 25.4% was within the clinically acceptable limits of 30% [4]. Similar results were demonstrated when TPUD was compared with Fick method [5] and flow probes.[6]

3.1.2 Qualitative and quantitative estimation of anatomical shunts

The characteristics of the indicator dilution curves generated by TPUD may be used for qualitative and quantitative estimation of anatomical shunts. Dilution curves representing right to left shunts (see fig. 3-4) exhibit a short appearance time (arrow 'a' on figure 3-4) and an abnormal upslope (arrow b) or an extra hump (arrow c). This is due to a part of the indicator bypassing the lungs through the shunt and reaching the arterial sensor earlier followed by the rest of the indicator.[7] In the case of left to right shunts, (see fig 3-5) dilution curves have a normal appearance time but there is more asymmetry of the downslope versus upslope than in the normal curves due to recirculation of the indicator (marked as arrow 'd'). Bi-directional shunts demonstrated characteristic properties of both types of shunt i.e. short appearance times and asymmetry of the downslope.

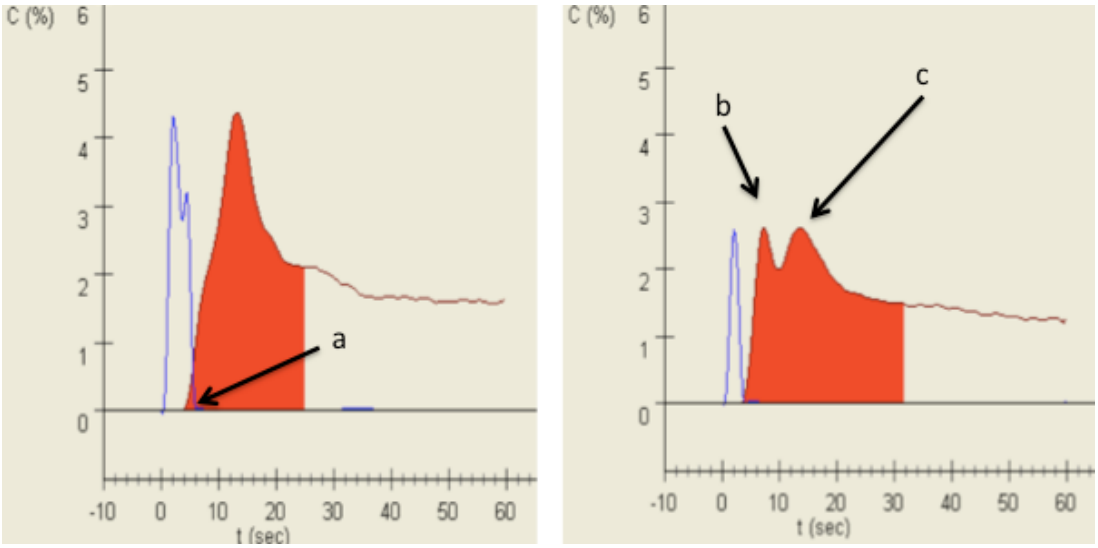

Figure 3-4 Dilution curve of right to left shunt after atrioventricular septal defect repair.Characteristic features include: (a) short appearance time (here an extra hump on the arterial curve begins before venous curve has finished), (b) an abnormal upslope, in this case resulting in a double peak, where (c) represents the normal peak resulting from indicator in the non-shunted blood. Reproduced with permission form Transonic, NY, USA.

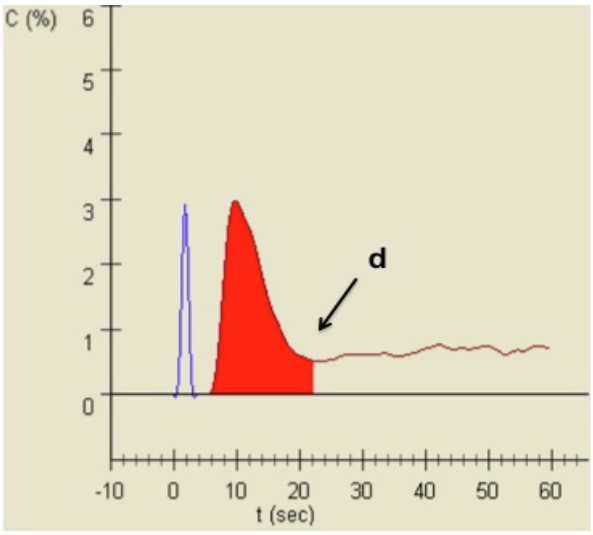

Figure 3-5 Dilution curve in left to right shunt after ventricular septal defect repair. Here there is a normal appearance time for the arterial curve, but asymmetry of the downslope (indicated as 'a').. Reproduced with permission form Transonic, NY, USA.

In addition to the qualitative shunt detection, the software also provides a quantitative estimate of the ratio between the pulmonary to systemic blood flow (Qp/Qs). This is derived via algorithms based upon the observed changes in the shape of the dilution curve due to the presence of anatomical shunts.[8,9] It compares the predicted area under a normal dilution curve with the area of the observed dilution curve. In right to left shunts the observed area of the 'hump' represents part of the indicator that bypasses lungs. Thus, the ratio of the rest of the area (from indicator that passed the lungs) to total area (including the 'hump') that was recorded in arterial gives a Qp/Qs ratio less than one. In the case of left to right shunt, the observed area under the curve is larger than the area of the predicted normal dilution curve due to the presence of saline recirculation, resulting in an abnormally extended downslope. Thus the ratio of observed area under dilution curve to predicted area gives Qp/Qs ratio greater than one.

3.1.3 Markers of preload

In addition to measuring CO and detection of anatomical shunts, TPUD also measures three novel static markers of preload (fig 2-4 in previous chapter) [2] :

(i) Total end diastolic volume index (TEDVI)

It is the sum of the end-diastolic volumes of the atria and ventricles (fig 3-6). The calculation is based upon the assumption that the major spread of the arterial vs venous curve is due to the indicator traveling through the heart chambers. It is indexed to body weight and the expected range is between 6-10ml/kg. (For our research, the volumetric data was allometrically scaled to body surface area using a power of 1.38 (i.e. $(m^2)^{1.38} = m^{2.6}$) (see chapter 2); hence volumes are expressed as $ml/m^{2.6}$.[10,11]

It is calculated by the following formula:

$$TEDV = CO \times (\frac{1.62}{HR} + 0.77 \times CHc)$$

where
CO: cardiac output
HR: heart rate and
CHc: $(CHart^2 - CHven^2)^{1/2}$
CHart and CHven are chords (width of the curve at one-half the maximum height of the curve) arterial and venous curves in minutes, respectively (fig, 2-4, 3-6).

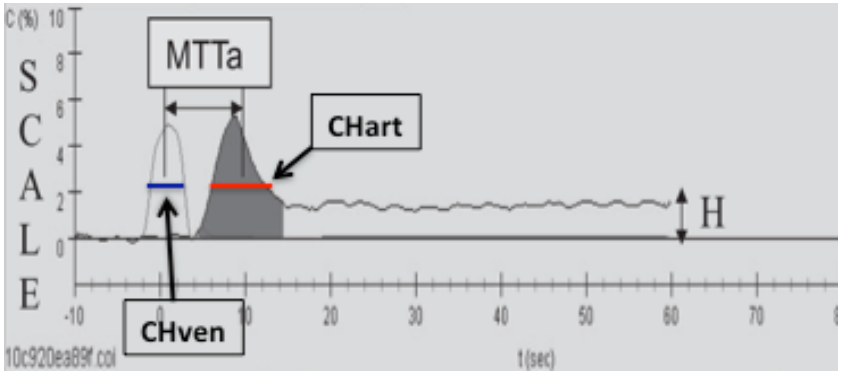

Figure 3-6 Changes in the blood saline concentration after indicator injection. 'Y' axis is the percent concentration of saline in the blood .'X' axis is the time. The concentration of injected saline becomes stable within 40-60 seconds from the time of injection (H). MTTa is the time during which the indicator travels form the injection site to the arterial sensor. Reproduced with permission form Transonic, NY, USA.

(ii) Central blood volume index (CBVI)

This is the volume of blood between the injection site (central vein) and the recording site (artery). Blood in the heart, lungs, and large vessels contributes to the majority of CBV. It is indexed to body weight with an normal value between 18-22 ml/kg (fig 2-4, 3-6).

It is calculated as follows:

$$CBV = CO \times (MTTa - MTTv - MTTt)$$

where

CO: cardiac output

MTTa: time during which the indicator travels from the venous sensor (injection site) to the arterial sensor

MTTv: mean transit time of the venous injection recorded by the venous sensor and

MTTt: mean transit time during which the indicator travels in the arterial loop before reaching the sensor. It is calculated as MTTt = $\frac{Va}{Qa}$ where V_a is the known priming volume of the tubing segment and Q_a is the known blood flow in the AV loop.

(iii) Active circulating volume index (ACVI)

This is defined as the volume of the blood in which the indicator mixes in one minute from the time of injection. ACVI is also indexed to body weight and the typical values are between 40- 60 ml/kg. ACV is calculated from the following formula:

$$ACV = \frac{Vinj}{H}$$

where

Vinj: volume of the injected saline in millilitres and

H: new level of isotonic saline concentration in blood at the end of the first minute after the venous injection recorded by the arterial sensor (fig 2-4, 3-6).

3.1.4 Main limitations of TPUD method

There are three major limitations for TPUD as described below:

1) The presence of intra or extra cardiac shunts may cause abnormalities of the dilution curve. [9,12] This may affect the accuracy of the CO measurement. However, this will be apparent on inspection of the dilution curve and the software also produces a related message on the monitor screen to notify the user.

2) TPUD is as prone to similar indicator loss errors as any other indicator dilution techniques. Though the venous sensor accurately measures the volume of the indicator injected, however, the loss may be due to multiple other reasons past the venous sensor for example dead space of the venous catheter or abnormal lung perfusion. This leads to loss of indicator resulting in overestimation of CO. Measurements involving central blood volume may also be inaccurate for the same reasons.

3) Although the amount of isotonic saline used as an indicator is small (0.5-1 ml/kg, max 30 ml) however, repeated measurements may lead to considerable volume injection and volume overload. This is especially relevant in small post cardiac surgical neonatal patients where cardiac function may be sensitive to excessive preload.

3.2 Pressure recorded analytical method (Mostcare^{TM}, Vytech Health, Padova, Italy)

Pressure recording analytical method (PRAM) is a minimally invasive, continuous monitoring (beat to beat) system based upon pulse contour analysis. Measurement involves connecting the pre-existing arterial line to the PRAM monitor via a standard disposable pressure transducer and a dual output electronic module. One output is fed into the standard bedside monitor, while the other one is connected to the PRAM monitor. The arterial pressure tracing is checked beforehand to exclude artefacts and ECG is monitored to confirm sinus rhythm.

3.2.1 Background and Description of PRAM technique for measuring cardiac output

Pulse contour methods convert pulse pressure to SV from the area under the pulse systolic portion of the pressure wave (i.e., from the start of the upstroke [aortic valve opening] to the dicrotic notch [point of aortic valve closure]) represented by 'P' in fig 3-7. This was based upon the classic '2 element Windkessel model' (see fig 1-6 on page 52) described initially by Otto Frank in1899 [13] and further refined by Westerhof [14] and Stergiopulous [15] to a 3 and 4 element model introducing impedance and arterial inertance respectively. This improved the accuracy of the algorithm for stroke volume estimation form the arterial pulse pressure curve.

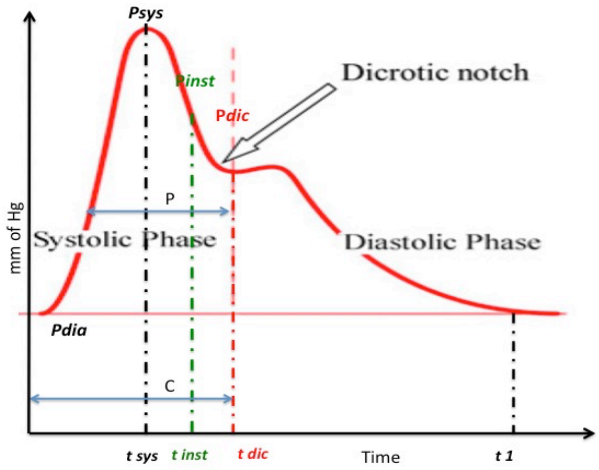

Figure 3-7 Arterial pressure waveform. 'P' is the pulsatile and 'C' is the continuous phase during systole. Reproduced from: Romano SM and Pistolesi M. Crit Care Med 2002; 30:1834-1841.[16]

PRAM is a pulse contour based method based upon the physics theory of perturbations, which states that each physical system under the effects of a stress tends to react to reacquire its own condition of stability (i.e. the situation of minimal energy required). PRAM also makes an assumption that volume changes in any vessel occur mainly because of the radial expansion in response to variations in pressure.[17] The interaction between these pressure and volume changes of arterial system is influenced by four main physical variables. Firstly, the force of the blood ejection generated by the left ventricle, second is the arterial impedance counteracting the pulsatile blood inflow, third is the arterial compliance and lastly, the peripheral vascular resistance generating backward reflections of the pressure wave depending on the heart rate and physical characteristics like diameter and stiffness of the arterial vessels downstream.[16] All these variables are dynamic, interdependent and require simultaneous evaluation for the estimation of CO. The relationship between all these factors is taken into account by a factor 'Z'.

Estimation of ‘Z’ either by predicted data from unrelated in vitro measurements or by calibration with an independent measurement of SV will enable measurement of stroke volume, hence CO.

PRAM differs from the rest of the pulse contour analysis methods in the following ways:

Firstly, it takes into account both the pulsatile and continuous contributions (P+C) of the physical forces underlying the relationship between pressure curve morphology and blood flow while estimating CO (fig 3-7).

Secondly, ‘Z’ is measured directly from the morphology of arterial pressure waveform without the use of predicted data or external calibrations against a reference method.

‘Z’ is calculated by PRAM as equal to $\left(\frac{P}{t}\right) \times K$

where

$\left(\frac{\mathrm{P}}{\mathrm{t}}\right)$ (mmHg/sec): the analytical description of the pressure wave profile as changes of pressure (P) with time (t) along each cardiac cycle

K: dimensional factor inversely related to the instantaneous acceleration of the vessel cross-sectional area.

‘K’ is calculated from the ratio between the expected (under physiologic conditions) and measured mean blood pressure. The denominator is variable and can change with each cardiac cycle. As a result, ‘K’ may vary with every cardiac cycle. The reference constant value at the numerator determines the magnitude of deviation from the normality of the mean arterial pressure. Two different values of the expected mean blood pressure are considered for estimation of ‘K’ depending upon the catheter position [central (100 mm hg) or distal artery (90 mm Hg)].[18] The value of ‘K’ will be affected by the presence of physical factors affecting the pressure wave transmission for example low stroke output from the left ventricle or backward wave reflections from the peripheral vasculature. This incorporates the deviation from physiology of the transmitted pressure wave during calculation of ’Z’.

Stroke volume is calculated as:

$$SV = \frac{A}{Z} = \frac{A}{\frac{P}{(t)} \times K}$$

where

A (mmHg x seconds): the whole area under the systolic portion of the pressure curve represented by 'P+C' (fig 3-7).

Estimation of P/t from the pressure wave assumes a dynamic equilibrium among various factors at the point of peak systolic pressure and the pressure at the dicrotic notch leading to arterial blood flow (fig 3-7).

$$\frac{P}{t} = \frac{(P_{sys} - P_{dia})}{t_{sys}} + \frac{P_{dic}}{(t_1 - t_{dic})} - \frac{P_{inst}}{(t_1 - t_{inst})}$$

where

P_{sys}, P_{dia}, P_{dic} and P_{inst} are peak systolic pressure, diastolic pressure, pressure at the dicrotic notch and pressure at any given instant of time respectively.

t_{sys} is the systolic time, t_1 is the total time of the cardiac cycle, and (t_1-t_{dic}) is the diastolic time. t_{inst} is the time at any given instant.

$\frac{P_{sys} - P_{dia}}{t_{sys}}$ represents the impulse generated by the left ventricular output in the vessel where the pressure is recorded,

$\frac{P_{dic}}{(t_1 - t_{dic})}$ is the pressure over time at the dicrotic notch mainly affected by the arterial properties like compliance, impedance and resistance .

Variations in the downslope between P_{sys} and P_{dic} as a result of backward reflections of the pressure wave from the periphery affects the characteristics and appearance of dicrotic notch

on the pulse wave. $\frac{P_{inst}}{(t_1 - t_{inst})}$ accounts for the changes in the morphology of the pressure curve as a result of these back reflections. P_{inst} is the pressure value occurring at the time (t_{inst}) of the relative maximum value of the second derivative of the pressure curve between P_{sys} and P_{dic} .

In addition, PRAM differs from other pulse contour methods in the frequency of sampling of data from the arterial tree. PRAM samples data at 1000Hz [19] as opposed to 100 Hz by other methods. This high frequency is considered useful for improving the accuracy of calculation of 'Z(t)' and stroke volume. The details of PRAM methodology is described in detail by Romano and Pistolesi.[16]

Calamandrei et al compared PRAM with Doppler echocardiography for measurement of CO in forty eight mechanically ventilated children. They reported significant correlation between the two methods (r^2=0.99, p<.01). The mean bias reported was 0.12$\pm$ 0.27 l/min.[20]

Similar results were reported by Romano and Pistolesi in their study involving twenty two adult patients comparing PRAM with Fick's and thermodilution method.[16]

3.2.2 Dynamic markers of fluid responsiveness measured by PRAM

In addition to measuring SV, PRAM also measures three dynamic markers of fluid responsiveness - systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV). Dynamic markers are measured on a beat-to -beat basis and are based upon the cyclical changes of the loading conditions of both the ventricles as a result of positive pressure ventilation. The magnitude of these respiratory changes can be used as a guide to predict fluid responsiveness.[21] A detailed description with literature review regarding the utility and limitations of these markers in predicting fluid responsiveness is described in Chapter 2.

3.2.3 Measurement of arterial dP/dt $_{max}$

Arterial dP/dt_{max} can be estimated from the pressure waveform obtained via peripheral arterial catheters. This is the maximum ascending slope of the arterial pressure waveform (fig 2-12 in chapter 2). This has been shown to correlate well with invasively measured intra-ventricular dP/dt_{max} in children [22] and act as a surrogate marker for estimating left ventricular contractility.

PRAM is able to provide an estimation of the arterial dP/dt_{max} continuously from the arterial pressure waveform. The only study estimating dP/dt_{max} by PRAM appears valid (despite being inaccurate for SVI) when compared to dP/dt_{max} derived from echocardiogram in adults.[23] A detailed description is provided in Chapter 2 (see section 2.5, page 137).

3.2.4 Limitations of PRAM

PRAM is prone to similar sources of error(s) as other pulse contour methods.

Quality of the recorded arterial pressure waveform: Since the estimation of SV is dependent upon characteristics of arterial pressure waveform, any factors affecting the quality of this recording will directly affect the accuracy of CO estimation. These may be either patient related or technical problems.

Arrhythmias, valvular or vascular disease process for example aortic regurgitation, aortic dissection or peripheral arterial stenosis can lead to inappropriate signal acquisition affecting the accuracy.

Technical factors commonly seen in intensive care settings or operating rooms are generally due to an inadequate response of the elastic fluid filled catheter and the pressure transducer system. This leads to under or over damped trace resulting in incorrect estimation of arterial impedance and stroke volume. Majority of these factors can be overcome by a careful evaluation of the arterial pressure waveform by the attending physician.

The accuracy of measured dynamic markers in the prediction of fluid responsiveness is further compromised in situations with small pleural pressure changes during the respiratory cycle for example spontaneous breathing patients, open chest conditions [24,25] or ventilation with small tidal volumes.[26] In addition, the influence of vasoconstrictors [27] and abdominal hypertension [28] on the utility of these markers is still debated.

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PART B

Chapter 4 Research Methodology

4.1 Aims

4.1.1 Validation study for PRAM

The hypotheses were:

(i) PRAM is as accurate as TPUD for measuring CO in children.

(ii) PRAM is able to accurately track changes in CO after routine therapeutic interventions with the use of polar plots.

4.1.2 Predicting fluid responsiveness from static and dynamic markers measured by TPUD and PRAM respectively and study the effect of baseline contractility on stroke volume in response to fluid bolus administration

The hypotheses were:

(i) Novel static and dynamic markers measured by TPUD and PRAM respectively are able to predict for fluid responsiveness in critically ill children in PICU setting.

(ii) Baseline myocardial contractility has a significant influence on the stroke volume response after fluid bolus administration.

4.1.3 Accuracy of TPUD method for identifying small anatomic shunts

We hypothesise that TPUD technique is accurate for identifying small anatomical shunts when compared with standard echocardiography.

4.2 Study design and population

The study was a prospective, non-randomised, single centre study conducted within a 20 bed, multi-disciplinary paediatric intensive care unit, at Evelina London Children's Hospital, London, United Kingdom.

Research application and ethics approval

The research idea was first presented to a local research group for peer review. Once approved, a formal application was made to the hospital research and development board on an online portal (Integrated research application system) with minor modifications based upon comments from peer review group. This was accompanied with a detailed study protocol, parent and child (elective admission only) information leaflets (see appendix), consent form (see appendix) and an application for research ethics approval. The regional ethics committee (South East London REC2, 10/H0802/62) approved the study after a short interview process.

Database for data capture

An electronic database was created on Microsoft access to capture the clinical data. The data was first recorded on paper printouts of the database at the bedside. This was due to two reasons (a) unavailability of computers at each bed space and (b) laptops will occupy more space in addition to the two existing monitoring devices (TPUD and PRAM) at the bed side and

may limit accessibility to the patient. The data was entered into the electronic database within 24 hours of conclusion of the case. Another research fellow checked all the data entries to minimise errors during transcription. Data from TPUD and PRAM was downloaded in an 'Excel' file through a data transfer module or a data card respectively. All data was kept on hospital computers and was password protected.

Case recruitment and consent

Patients fulfilling or likely to fulfil the inclusion criteria were identified during their stay in PICU or from the cardiac wards through daily operating lists. Parents were approached by a member of the research team (comprising of two research fellows and a nurse) for obtaining written informed consent for the study. All the members of the team were GCP (good clinical practice) trained. The timing of the consent depends upon the nature of the admission to the intensive care unit. For elective admissions (for example cardiac surgical patients), parents were approached during pre- operative assessment, which is typically between 24-72 hours before the day of the surgery in majority of the cases in our institute. Consent was obtained as soon as possible after the admission to intensive care unit in emergency cases once the patient qualifies as per the inclusion criteria (mentioned below). Data was collected within the first 24 hours following admission to the intensive care unit.

Inclusion and exclusion criteria

Inclusion criteria were (i) weight >2kg, (ii) age <16 years and (iii) pre-existing arterial and central venous lines.

Children with (i) significant valvular regurgitation, (ii) large anatomical shunts, (iii) extreme haemodynamic instability, or (iv) arrhythmias (v) residual left sided obstructive lesions (e.g. aortic stenosis, coarctation) were excluded from the study. Severe valvular regurgitation and large anatomical shunts were excluded by trans thoracic echocardiography. Extreme

hemodynamic instability was defined as either of the following occurring in the 30 minute period before advanced hemodynamic variables were measured: (a) ongoing fluctuations in the bedside hemodynamic variables of heart rate and/or blood pressure and/or central venous pressure greater than approximately 20% of baseline, or (b) requirement for an increase in inotropic or vasopressor support, greater than an increment of 5 mcg/kg/min for dopamine or 0.05 mcg/kg min for adrenaline or noradrenaline. All children had continuous ECG monitoring prior and during the course of the study to confirm sinus rhythm.

Study subjects

A total of one hundred, mechanically ventilated children (64 males) were enrolled into the study between September 2010 to May 2012. The median (IQR) age and weight were 18 (6-48) months and 10 (5.6 - 15) kg, respectively.The majority of patients enrolled were post cardiac surgery with different aetiologies. The patient diagnostic characteristics are shown table 4-1.

The number of participants for the validation of PRAM (48 children) and determination of accuracy of TPUD for detection of small anatomical shunt (73 patients) were subset of the total study population of 100 children recruited to assess the predictive ability of static and dynamic markers for fluid responsiveness. Children were enrolled consecutively (after consenting) as there was no randomisation.

Table 4-1 Patient diagnostic characteristics (all patients).

Diagnosis	Number of Patients
Post Cardiovascular surgery	90
VSD	17
TCPC	17
TOF	10
AVSD	9
TAPVD	7
CoA	5
Others	25
Respiratory	2
Sepsis	8
Total	100

VSD: Ventricular septal defect; TCPC: Total cavopulmonary connection; TOF: Tetralogy of Fallot; AVSD: Atrioventricular septal defect; TAPVD: Total anomalous pulmonary venous drainage; CoA: Coarctation of aorta.

4.3 Study protocol

The following section provides a brief overview of the study protocols for the three research aims listed before. A more detailed description of the protocol including statistical methods for each of the studied aims is described in individual corresponding chapters 5-7.

Study protocol for:

(i) Validation study for PRAM and

(ii) Assessment of the predictive ability of the static and dynamic markers measured by TPUD and PRAM respectively, for fluid responsiveness

Paired haemodynamic measurements using TPUD and PRAM were made as soon as possible after the patient was admitted to the PICU. Baseline demography and physiological data were also collected.

The paired measurements were made before (up to 15minutes) and after (up to 30 minutes) therapeutic interventions aimed towards augmentation of cardiac output (for example 10ml/kg of 0.9% Saline or Hartmann's solution over 20 minutes, initiation or augmentation of dose of inotrope). The attending physician made the decision regarding the timing and choice of intervention on the basis of the available clinical information. They were blinded to the advanced haemodynamic measurement data.

An average of at least two consecutive TPUD measurements were taken. A third measurement was only obtained if the shape of the injection or dilution curves was unsatisfactory (fig 3-3,) or if the variation between the two measurements was greater than 20%. In addition to CO and CI, data was also recorded for the three novel preload markers TEDVI, CBVI and ACVI measured by TPUD.

PRAM measurements could not be obtained exactly at the same time as the TPUD measurements required interruption of the arterial line. Thus, an average of the continuous

PRAM measurements (CO, CI, PPV, SPV, SVI and dP/dt_{max}) was obtained for 3 minutes before and after the time corresponding to the TPUD measurements for comparison.
The study protocol(s) is shown in fig 4-1.

The set of paired measurements was repeated approximately 5-20 minutes after initiation of CO augmenting interventions (fluid bolus administration or initiation or increase of inotropic therapy). A positive response was described as an increase in stroke volume index $\geq$15% after the fluid bolus or change in inotrope therapy.

Repeated sets of paired measurements on these patients enabled (i) comparison of the cardiac output and index measured simultaneously by TPUD and PRAM and (ii) assessment of the ability of PRAM to track changes in CO in response to these interventions. A maximum of five combined sets (pre and post intervention) were taken on each patient during the course of their admission.

There was a time lag of approximately 8-10 minutes from the decision to administration of CO augmentation therapy due to the TPUD and PRAM measurements. Hence, measurements were only performed for episodes where the attending physician considered this time lag to be safe, taking the clinical condition of the child into consideration. However, on few occasions, child's clinical condition warranted immediate treatment and hence measurements were not performed. We did not collect the data to quantify such events.

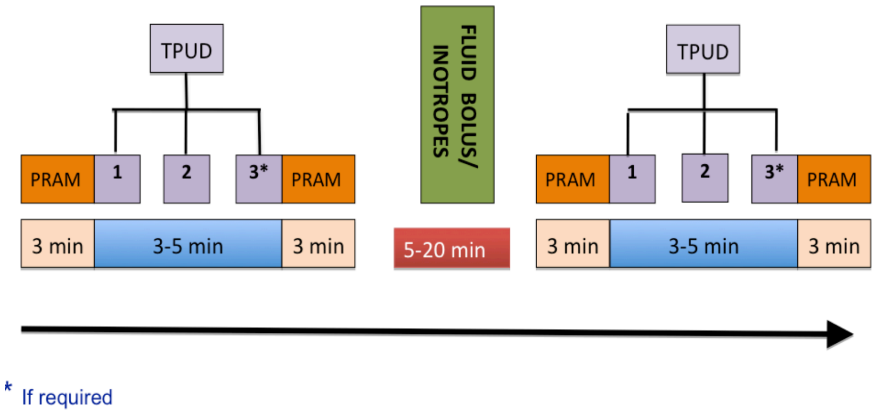


Figure 4-1 Study protocol for (a) validation of PRAM and (b) assessment of the predictive ability of the static and dynamic markers for fluid responsiveness.

(ii) Study protocol for assessment of accuracy of TPUD for diagnosis of anatomic shunt

TPUD measurements were performed simultaneously with 2D echocardiography in 73 children. TPUD diagnosed and classified shunts as either right to left or left to right or bidirectional depending upon the characteristic changes in the dilution curve as explained in chapter 7.

In addition to the qualitative analysis, TPUD software also provided a quantitative estimate of the ratio between the pulmonary to systemic blood flow (Qp/Qs) as described in chapter 3. Briefly, this is derived via algorithms based upon the observed changes in the shape of the dilution curve due to the presence of anatomical shunts.[1-3] Comparing the predicted area under a normal dilution curve with the area of the observed dilution curve derives Qp/Qs.

Procedure for validating shunt detection

Echocardiography was considered as the reference method for shunt detection in our study. An experienced operator performed a single, detailed 2D echocardiographic scan when clinically indicated. Conventional echocardiographic methods were employed to detect residual shunts

including cross-sectional echocardiography coupled with pulsed wave, continuous wave and colour flow Doppler assessment of any residual shunts. These techniques allowed determination of direction of the shunt (right to left, left to right or bidirectional) but they cannot reliably quantify Qp/Qs in this setting. The operator described the shunt size as:

“tiny” if there was only a narrow jet of flow on colour flow Doppler which was not visualized on cross-sectional imaging alone,

“small” if the shunt jet appeared wider than 2mm and if a residual shunt could be visualized without colour flow Doppler.

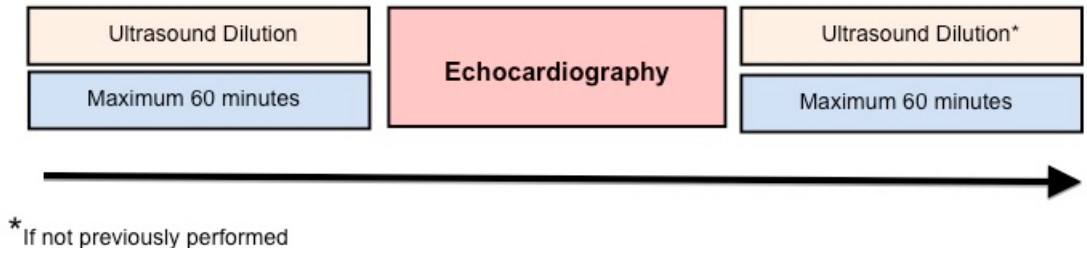
“moderate to large”, where a shunt was not pressure restrictive and which appeared hemodynamically significant by volume loading of cardiac chambers.

In case of poor image quality due to absence of good acoustic windows in some of our patients (immediate post cardiac surgery) two experienced observers, blind to the TPUD results, agreed the final echocardiographic findings.

All TPUD measurements taken for different reasons within one hour on either side of the echocardiogram were considered as eligible for shunt detection (fig 4-2). A minimum of one set of TPUD measurements (on either side of an hour of echocardiogram) was required as part of the study protocol.

Additional sets of TPUD measurements were also performed when therapeutic manoeuvres were made for clinical indications within the stated time window (for example, administration of a fluid bolus or addition of a vasoactive agent).

Each set of TPUD measurements required generation of good quality dilution curve. In case the quality of the curve is compromised due to any reason (see fig 3-3 on page 160), indicator injection was repeated until at least two analysable curves were produced. Ultrasound dilution was considered to have identified a shunt only if two or more measurements within a set suggested presence of the shunt. In all cases, operators performing both echocardiography and TPUD were blinded to the results from the other technique.



*If not previously performed

Figure 4-2 Study protocol for detection of anatomical shunt by TPUD.

4.4 Research publications and presentations

Various aspects of the work have been presented at various national and international platforms enabling sharing of our findings and research ideas with the scientific community with similar interests. The details of the presentations and publications arising as a result of this research study are listed below:

Publications

(i) Saxena R, Steeley S**,** Durward A, Murdoch I and Tibby S Predicting fluid responsiveness in 100 critically ill children: the effect of baseline contractility.
(*Intensive Care Med* 2015 Dec;41(12):2161-9. doi: 10.1007/s00134-015-4075-8)

(ii) **Saxena R**, Durward A, Murdoch I and Tibby S. Accuracy of transpulmonary ultrasound dilution (co-status™) for identifying anatomic shunts.
(*J Clin Monit Comput*. 2015 Jun; 29(3):407-414 .DOI: 10.1007/s10877-014-9618-y. PMID: 25240251)

(iii) **Saxena R,** Durward A, Murdoch I and Tibby S. Comparison between Transpulmonary ultrasound dilution and Pressure recording analytical method for measuring Cardiac output in children.
(*Br J Anaesth.* 2013 Mar;110(3):425-31).

Presentations

(i) **Saxena R ,** Durward A, Murdoch I and Tibby S. Prediction of stroke volume response to fluid bolus in 100 children. Poster presentation at 33rd International Symposium on Intensive Care and Emergency Medicine, Brussels, March 2013.
(Abstract: Crit Care 2013, Volume 17 (Suppl 2): S78)

(ii) **Saxena R,** Durward A, Murdoch I and Tibby S Accuracy of transpulmonary ultrasound dilution (CO-Status™) for identifying anatomic shunts. Short oral presentation at European Society of Paediatric and Neonatal Intensive Care Meeting, Hannover, Germany, 3 Nov 2011.

(*Abstract: Intensive Care Med 2011, Volume 37 Supplement 2: S345)*

(iii) **Saxena R,** Durward A, Murdoch I and Tibby S. A comparison between novel static and dynamic markers of fluid responsiveness - preliminary data from 47 children – Oral presentation at European Society of Paediatric and Neonatal Intensive Care Meeting, Hannover, Germany, 3 Nov 2011.

(*Abstract: Intensive Care Med 2011, Volume 37 Supplement 2: S344)*

(iv) **Saxena R,** Durward A, Murdoch I and Tibby S. Comparison between Transpulmonary ultrasound dilution and Pressure recording analytical method for measuring cardiac output in children. Oral presentation at the European Paediatric Cardiac Intensive Care Society Meeting, Cambridge, UK, September 2011.

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Chapter 5 Pressure Recording Analytical Method for measuring cardiac output in critically ill children: a validation study.

Saxena R, Durward A, Puppala NK, Murdoch IA, Tibby SM

Br J Anaesth. 2013 Mar;110(3):425-31

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5.1 Abstract

Background

Pressure Recording Analytic Method is a novel, arterial pulse contour based method for measuring cardiac output (CO). Validation studies of PRAM in children are few, and have not assessed both absolute accuracy and ability to track changes in CO across a broad case mix. We aimed to compare CO as measured by PRAM with that using a transpulmonary dilution method in a cohort of critically ill children.

Methods

Forty eight, mechanically ventilated children with a median (interquartile) weight of 10.7 (5.5 - 15) kilograms with arterial and central venous catheters in situ were studied. Cardiac output (CO) was measured simultaneously using PRAM and the comparator method, transpulmonary ultrasound dilution (TPUD). Measurements were repeated before and after therapeutic interventions that were intended to augment CO (for example, fluid bolus).

Results

In total, 210 paired measurements were compared. The mean (SD) CO was 1.9 $\pm$ 1.2 L/min with TPUD as compared to 1.92 $\pm$ 0.5 L min^{-1} using PRAM. The mean bias was 0.02 L/min with wide limits of agreement: $\pm$ 2.21 L min^{-1}, giving a percentage error of 116%. The concordance between PRAM and TPUD for measuring changes in CO was also poor, with only 37% of measurements falling within the pre-defined polar plot limits of $\pm$ 30 degrees.

Conclusion

There is an unacceptably poor agreement between TPUD and PRAM. We do not recommend the use of PRAM for measuring CO in critically ill children with the current algorithm.

5.2 Introduction

Cardiovascular organ failure is common in critically ill children.[1 2] Compared to adults, children manifest both a higher incidence of cardiovascular dysfunction, and greater variability in haemodynamic status during resuscitation; furthermore, these changes can occur rapidly.[3] Early detection of cardiovascular insufficiency in high-risk patients may reduce morbidity and mortality, by guiding the timely application of appropriate therapy.[4 5] However, an accurate assessment of cardiovascular status requires advanced haemodynamic monitoring, including measurement of cardiac output (CO).[6 7] This is reinforced by the finding that CO cannot be estimated clinically, and deleterious changes in CO can precede changes in other haemodynamic variables.[8 9]

Although a variety of techniques for CO measurement are available in paediatric patients, there is growing interest in continuous methodologies based upon arterial pulse wave analysis. These have the obvious advantage of utilising a pre-existing arterial line; in addition, not all require external calibration.[10] However, concerns have been raised about the accuracy of these methods, particularly during periods of haemodynamic instability.[11 12]

Pressure recording analytic method (PRAM) is a relatively novel arterial pulse wave method of CO measurement.[13] In contrast to other pulse contour techniques, PRAM is based primarily upon detailed morphological analysis of the pressure waveform, including identification of pulsatile and non-pulsatile systolic pressure-time areas together with an estimation of vascular impedance. There are several adult and animal validation studies of PRAM; however there is paucity of literature regarding its use in paediatrics.[14 15]

With this in mind, we aimed to validate PRAM in a heterogeneous group of critically ill paediatric patients, by comparison with a transpulmonary dilution method for CO measurement. The latter have recently been described as approaching a gold standard for bedside paediatric measurement.[16] Our aims were twofold: first to compare absolute values for the two techniques via Bland Altman analysis, and second to evaluate whether PRAM could track changes in CO after routine therapeutic manoeuvres, via use of Polar plots. [17]

5.3 Methods

This prospective, single centre, observational study conducted within a 20 bed multi-disciplinary paediatric intensive care unit. The study was approved by the regional ethics committee (South East London REC2, 10/H0802/62) and written informed consent was obtained from all parents or legal guardians.

Forty eight, mechanically ventilated children (32 males) were enrolled during September 2010 to October 2011, of whom 78% were also receiving inotropic support. The median (IQR) age and weight were 17.0 (4.5 – 47.3) months and 10.7 (5.5 - 15) kg, respectively. The majority of patients were admitted following cardiac surgery (table 5-1), and data were collected within the first 24 hours following admission. Inclusion criteria included presence of arterial and central venous lines. Children with significant valvular regurgitation, extreme haemodynamic instability, large anatomical shunts, arrhythmias and residual left sided obstructive lesions (e.g. aortic stenosis, coarctation) were excluded from the study.

Table 5-1 Patient diagnostic characteristics for validation of PRAM

Diagnosis	Number of Patients (%)
Post Cardiovascular Surgery	42(87.5)
VSD	10
TCPC	8
AVSD	3
TOF	3
TAPVD	5
Others	13
Respiratory	2(4.2)
Sepsis	4(8.3)
Total	48

VSD: Ventricular septal defect; TCPC: Total cavopulmonary connection; AVSD: Atrioventricular septal defect; TOF: Tetralogy of Fallot; TAPVD: Total anomalous pulmonary venous drainage.

5.3.1 Transpulmonary Ultrasound dilution technique

Transpulmonary ultrasound dilution (TPUD) (CO-Status^{TM}–Transonic systems, Ithaca, NY, USA) is an indicator dilution method. It utilises an extra-corporeal arterio-venous loop and two reusable ultrasound sensors: one on each side of the loop. A roller pump provides a constant blood flow rate in the AV loop. Normal saline (0.5 - 1ml/kg, max 20ml) at body temperature is used as an indicator. The transit times of the ultrasound beam crossing the extracorporeal tube change when saline is injected, in proportion to the amount of dilution of blood by the saline (the typical ultrasound velocities through 0.9% saline and blood are 1533 and 1580 m/sec, respectively), which are used to calculate CO via the Stewart-Hamilton equation.[18] This is an accurate and validated technique for measurement of CO in children and paediatric animal models.[19-21] The theory and in vitro validation of this technique is reported in detail by Krivitsky and co-workers.[22]

5.3.2 Pressure recorded analytical method

PRAM (Mostcare®- Vytech Health®, Padova, Italy) is a minimally invasive continuous (beat to beat) monitoring system utilising a form of pulse contour analysis. Measurement involves connecting the pre-existing arterial line to the PRAM monitor via standard disposable pressure transducer (Edwards life sciences, Irvine, CA, USA) and a dual output electronic module (Agilent, Technologies, Germany). One output is fed into the standard bedside monitor, while the other is connected to the PRAM monitor. All the arterial pressure tracings were checked beforehand to exclude artefact. The ECG was monitored to confirm sinus rhythm. A detailed description of the PRAM technology is found elsewhere.[23]

5.3.3 Study Protocol

Measurements were made as soon as possible after patients were admitted to the PICU (all within 24 hours of admission). Baseline demographic and physiological data were collected at the time of CO measurement. The study protocol is shown in figure 4-1.

Paired TPUD and PRAM measurements were made as follows: Two consecutive TPUD measurements were made, and the dilution curves inspected. If the shape of the injection or dilution curves were unsatisfactory (see figure 3-3), or if the variation between the two measurements was greater than 20%, a third measurement was obtained. The readings were than averaged. This process typically took 3-5 minutes. PRAM measurements could not be obtained exactly at the same time, as the TPUD measurements required interruption of the arterial line. Thus, we averaged the continuous CO from PRAM for 3 minutes before and after the time corresponding to the TPUD measurements. Thus, a complete set of comparative measurements took approximately 10 minutes. Heart rate was monitored continuously and non invasive blood pressure measurement performed every minute to ensure haemodynamic stability during this 10 minute period.

We performed repeated comparisons (as above) when patients received therapies likely to augment CO, such as fluid bolus administration or initiation of vasoactive medications. By taking repeated measurements on patients, we were also able to assess the ability of PRAM to track changes in CO.

5.3.4 Statistical Methods

Values for CO are reported as mean $\pm$ SD. Repeatability of each technique is reported via the coefficient of variation (standard deviation / mean, expressed as a percentage). Agreement between the two methods for measuring absolute values of CO was quantified using Bland Altman analysis.[24] Bias was defined as the mean difference between the two methods (PRAM

minus TPUD). Limits of agreement were calculated as mean bias ± 1.96 SD of the bias, adjusted for multiple measurements per patient.[24] Percentage error was calculated as (1.96 SD of bias / mean of reference method). We stipulated that the acceptable limits of agreement should be up to ± 26%. This was derived using animal data from de Boode and colleagues, who demonstrated a combined precision error for TPUD and surgically placed flow probes of 13.9%.[21] Assuming a precision of approximately 5% for flow probes yields a likely precision for TPUD of 13% ($\sqrt{[13.9^2 - 5^2]}$).[25] If we stipulate that PRAM should be at least as accurate as TPUD, we thus expect an upper limit for the combined limits of agreement of ± 26%.

Agreement between the two methods for tracking changes in CO (ΔCO) was quantified using polar plots.[16] This methodology is illustrated briefly in figure 5-1, and in more detail elsewhere.[17] [26] After exclusion of data points representing small changes in CO (i.e. vectors less than 10% of the mean Δ CO, equating to changes of less than 0.2 L min^{-1} in our study), we quantified tracking in two ways. First, acceptable calibration was defined as an angular mean bias of less than ± 5^o [17]. Second, we reported the percentage of data points lying within radial limits of ± 30^o from the polar axis. This area should contain approximately 95% of the data points if the test method is able to track changes in CO accurately.

Statistical analyses were performed using Stata v11 (StataCorp Texas), Microsoft Office Excel 2007 and polar plots were created using Sigmaplot 8.02 for Windows (Systat Software, Inc, San Jose, CA).

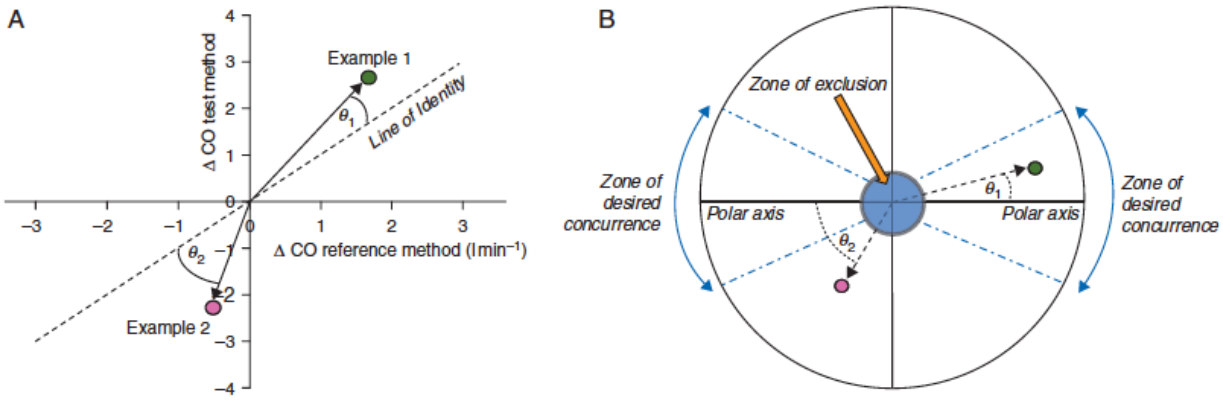

Figure 5-1 Explanation of Polar plots.(A) A hypothetical change in cardiac output (CO), as measured by two methods. If both methods concur exactly, the vector representing the change will lie on the line of identity. In example 1, the test method is over-reading the increase in CO compared to the reference method by 1 L min^{-1}. The vector representing this relationship will have an angle θ_1 that has a positive deviation from the line of identity. This is represented on the polar plot (B), whereby the angle θ_1 is represented relative to the zero degree axis, and the size of the vector is relative to the hypotenuse of the change in CO from the two methods. For a decrease in CO, as seen in example 2, where the test method also overestimates the negative change in CO (θ_2), the corresponding polar plot vector will be relative to the 180 degree axis (B). Good concurrence is represented by 95% of the points lying within an absolute deviation of ± 30 degrees from the polar axis (0 to 180 degrees, blue dashed lines). It is also customary to exclude small changes in CO, identified as those lying within the circular zone of exclusion. Typically this boundary represents changes in CO that are less than 10% of the mean change (blue shaded circle). Here example 1 shows adequate concurrence (within the ± 30 degree boundary from the polar axis, whereas example 2 does not.

5.4 Results

A total of 210 paired measurements using TPUD and PRAM, were compared in 48 children. Six children had two comparisons, 3 had three comparisons, 21 children had four and 18 patients had five or more comparisons. No child had more than eight comparisons. Repeated measurements on the same patient were made for the following reasons: fluid bolus (84%), administration of a vasoactive agent (8%) and extubation (8%).

The mean CO with TPUD was 1.9 ± 1.2 L min-1 as compared to 1.9 ± 0.5 L min^{-1} using PRAM. For cardiac index, the values were 3.8 ± 1.3 and 4.2 ± 1.8 L min^{-1} m^{-2} for TPUD and PRAM, respectively. The mean (SD) coefficient of variation for TPUD was 5.7 ± 6%. To quantify haemodynamic stability across each measurement epoch, we also calculated the coefficient of

variation for PRAM (by comparing the mean readings of each 30 second epoch, including both pre- and post-TPUD readings: this gave a mean (SD) coefficient of variation of 9.1 ± 6.2%.

Bland Altman analysis (figure 5-2) gave the mean bias of 0.02 L min^{-1}, with wide limits of agreement of ± 2.21 L min^{-1} and a percentage error of 116%. The Bland Altman plot suggested presence of a systematic error, with PRAM over reading at lower CO and under reading at high CO (figure 4, r = 0.69).

Since CO is a measure of total flow, which is influenced by patient size we repeated the analysis after normalisation to body surface area (i.e. cardiac index) to see if the error was influenced by high or low flow states. Here the mean bias was 0.95 L min^{-1} m^{-2} with very wide limits of agreement of ± 5.78 L min^{-1} m^{-2}, and an overall percentage error of 143% (figure 5-3). This suggested a different type of systematic error, heteroscedasticity, which persisted even after log transformation (data not shown).

The polar plots demonstrated a poor ability of PRAM to track changes in CO (figure 5-4). On average, PRAM followed the change in CO (mean angular deviation from polar axis of -5.4 degrees), however only 36.6% of measurements fell within the polar limits of ± 30 degree.

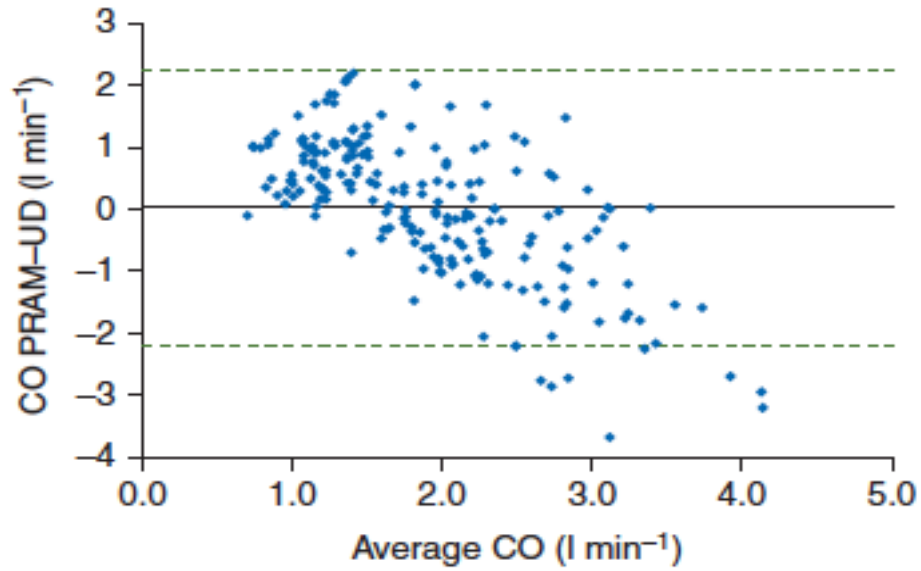

Figure 5-2 Bland Altman analysis for cardiac output as measured by transpulmonary ultrasound dilution and PRAM.

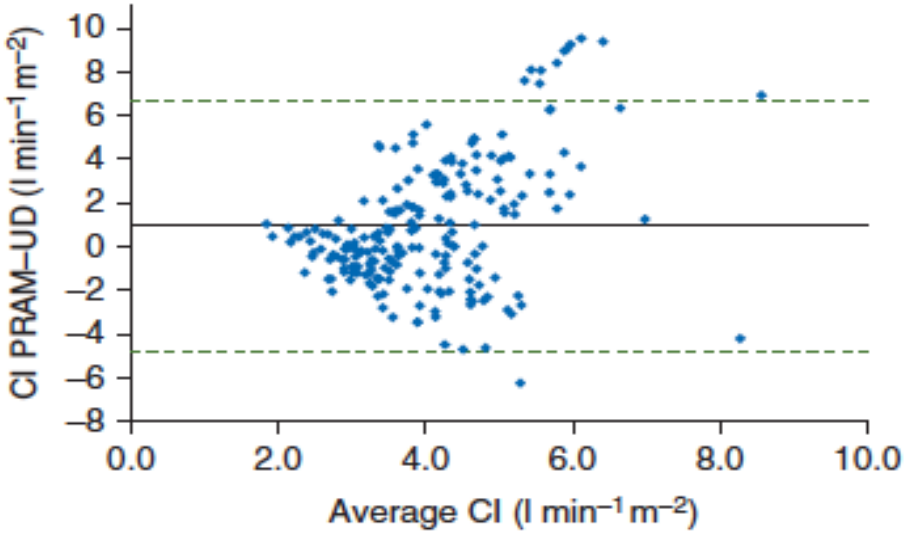

Figure 5-3 Bland Altman analysis for cardiac index as measured by transpulmonary ultrasound dilution and PRAM.

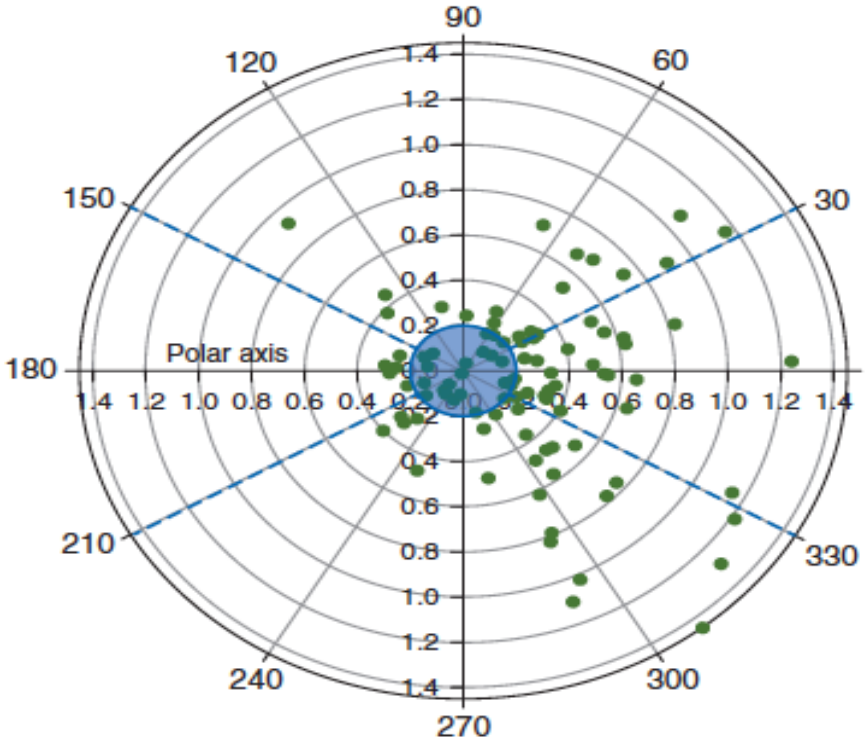

Figure 5-4 Polar plot demonstrating agreement between transpulmonary ultrasound dilution and PRAM for tracking changes in cardiac output. The small, bold circle indicates the zone of exclusion, whereby changes in cardiac output are too small to assess accurately. Hence data points lying within this circle are disregarded. Elsewhere, good agreement in tracking change in cardiac output is measured by the proportion of data points falling within the polar limits of ± 30 degrees (bold, blue dotted lines) from the polar axis.

5.5 Discussion

Our results demonstrate poor agreement between PRAM and TPUD, both in terms of measuring absolute CO (percentage error 116%) and tracking changes in CO (36.6% of measurements falling within polar limits). Our findings are at odds with the other two paediatric studies using PRAM. Calamandrei and colleagues compared PRAM with Doppler echocardiography in 48 children in a general PICU setting.[14] They reported a mean bias of 0.12 L min^{-1}, with limits of agreement of ± 0.65 L min^{-1}, giving a percentage error of 25%. Ricci and co-workers compared PRAM with pulmonary artery thermodilution in 25 cardiovascularly stable patients undergoing diagnostic cardiac catheterisation. Here the mean bias and limits of agreement were 0.2 ± 0.94 L min^{-1}, with a calculated percentage error of 45%.[15]

There are a number of potential reasons for the discrepancy between our results and these studies, including: use of different reference methods for CO, case mix, and different cardiovascular profiles.

Reference methods

We used ultrasound dilution as the reference method, which although a novel technique, has been shown to be accurate in small patients. In a piglet model using pulmonary artery flow probes as the reference method (a true gold standard), de Boode showed that the percentage error for TPUD was 27% (mean CO 0.96 L/min).[21] Similar accuracy (percentage error 24%) was shown in another swine model, using pulmonary artery thermodilution as the reference.[27] In 28 children undergoing cardiac catheterisation Crittendon compared TPUD with pulmonary artery thermodilution, again yielding a similar percentage error of 25.4%.[19] We have no reason to suspect that TPUD is any less accurate in our study; this is further supported by our low coefficient of variation (5.7%).

Case Mix and cardiovascular profiles

Our patient population contained potentially important differences to both prior paediatric studies. Ours was comprised primarily of children post cardiac bypass, a group not represented in either previous study.[14 15] Our median patient age was approximately half that of Ricci (2 versus 4 years). Despite having a similar age to that of Calamandrei, our median CO was approximately 30% lower (1.9 versus 2.7 L min^{-1}), suggesting a low flow state, as is typically seen post cardiac surgery. We have no information on vasoactive agent usage between the three studies, but these are likely to be very different given the differing case mix.

Our results do agree with recent adult studies. Paarmann and others compared PRAM with pulmonary artery thermodilution in 23 adult patients on the first post –operative day after cardiac surgery.[28] They reported an error of 87% with wide limits of agreement of $\pm$ 4.53 L min^{-1}. Biais and colleagues, in a study involving 35 adult patients, compared PRAM with transthoracic echocardiography at baseline and after volume expansion.[29] They showed a bias of -0.1 L min^{-1}

and limits of agreement of 1.9 to -2.1 L min^{-1} with percentage error of 34% at the baseline. Similar to our results they also demonstrated PRAM to be unable to accurately track changes in CO (concordance rate of 60%).

Our study has several possible limitations. Firstly, PRAM CO was not measured precisely at the same time as TPUD. Instead, PRAM readings were averaged 3 min before and after the time corresponding to the TPUD measurement. This was because the arterial line connection to the PRAM was interrupted during measurement of CO using TPUD. However, we believe that this is unlikely to have compromised our results due to unexpected haemodynamic instability, as the entire measurement period was brief (typically less than 10 minutes), PRAM readings were averaged pre- and post-TPUD and the average coefficient of variation for PRAM from each measurement period was 9.1± 6.2 %, which infers haemodynamic stability. The coefficient of variation for TPUD was 5.7 ± 6% which is in agreement with another study.[30]

Secondly, we did not measure the arterial line dampening coefficient while using PRAM. This represents a potentially important limitation, as both under- and over-dampening have recently been shown to adversely affect the ability of PRAM to estimate CO.[31] However, we are currently undertaking a follow on study evaluating factors that may affect accuracy of the PRAM algorithm, which includes measurement of the dampening coefficient.

A final point to consider is that there may be inherent limitations with the use of continuous pulse contour methods unique to the paediatric population. These methods typically estimate stroke volume from the arterial pressure waveform taking into consideration vascular properties such as impedance, compliance and peripheral vascular resistance. However paediatric studies have shown that these vascular properties may be age dependent, and can change rapidly during the course of illness. [3 32 - 33] Furthermore measuring small values in tiny children may push these devices towards their limits of accuracy.

5.6 Conclusion

In conclusion, we found an unacceptable lack of agreement between TPUD and PRAM for measurement of paediatric CO in critically ill patients. PRAM was also not able to track changes in CO accurately as compared to the TPUD method. Hence we do not recommend the use of PRAM for measuring CO in critically ill children with the current algorithm.

Declaration of Interests: None

Acknowledgement: PRAM hardware (Mostcare®) was provided by Vytech Health®, Padova, Italy. Transpulmonary ultrasound hardware (CO-Status™) and disposables were provided by Transonic systems, Ithaca, NY. There were no other commercial funding sources for this study.

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Chapter 6 Predicting fluid responsiveness in 100 critically ill children: the effect of baseline contractility

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6.1 Abstract

Purpose

Fluid overload is a risk factor for poor outcome in intensive care; thus volume loading should be tailored towards patients who are likely to increase stroke volume. We aimed to evaluate the paediatric predictive ability (stroke volume increase $\geq$15% after fluid bolus) of novel and established volumetric and dynamic haemodynamic variables, and assess the influence of baseline contractility on response.

Methods

We assessed 142 volume loading episodes (10 ml/kg crystalloid) in 100 critically ill ventilated children, median (interquartile) weight 10 (5.6 – 15) kg. Eight advanced haemodynamic variables were assessed using two commercially available devices. Systemic ventricular contractility was measured as the maximum rate of systolic arterial pressure rise.

Results

Overall, predictive ability was poor, with volumetric variables performing better than dynamic (area under receiver operating characteristic curves ranged from 0.53 to 0.67). The best predictor was total end diastolic volume index; however this did not increase in a consistent way with volume loading, with change post volume being weakly related to baseline values ($r = -0.19$, $p = 0.02$). A multivariable model quantified the importance of contractility on stroke volume response. Children with high baseline contractility, ($\geq 75^{th}$ centile), typically achieved a positive stroke volume response when end diastolic volume values changed by 10 to 15 ml/m$^{2.6}$, whereas patients with low contractility ($\leq 25^{th}$ centile), typically required end diastolic volume increases of 35 to 40 ml/m$^{2.6}$.

Conclusions

Current paediatric predictors of volume response perform poorly; prediction may be improved if baseline contractility is taken into account.

Take home message

The majority of advanced haemodynamic variables (volumetric and dynamic) have poor to moderate predictive ability in children in terms of the stroke volume response to fluid boluses. Baseline contractility is an important factor influencing patients' response to fluid volume loading. A patient with poor baseline contractility will need to increase their end diastolic volume by an increment that is 3 to 4 times greater that of a patient with good contractility to be able to increase stroke volume $\geq$15%.

Tweet

Advanced haemodynamic variables are poor predictors of fluid response in critically ill children. This improves when contractility is factored in

Keywords

cardiac output, fluid responsiveness, contractility, paediatric

6.2 Introduction

Fluid resuscitation may increase cardiac stroke volume in critically ill patients with sub-optimal preload [1]. However, this carries risk, as overzealous fluid administration can lead to fluid overload with deleterious consequences on patient outcome [2–4]. Approximately 40-60% of patients will typically respond to fluid therapy, by increasing cardiac output >10-15% [5, 6]. Thus, the ability to predict which patients will respond may obviate the need for unnecessary fluid administration.

The past two decades have witnessed development of several haemodynamic variables aimed at predicting fluid responsiveness [5 – 10]. Broadly speaking, these are classified as static and dynamic. Static variables are typically volumetric, and estimate either (i) maximal ventricular volumes, found at end diastole, or (ii) an aspect of intravascular volume; both are commonly derived using indicator dilution techniques [11]. Dynamic variables rely on the principle that cyclical changes in preload occur during the ventilatory cycle, which translate into changes in stroke volume via the Frank-Starling mechanism: the greater the change, the higher the likelihood of volume response.

Early enthusiasm for the predictive ability of these variables has been tempered by later studies, which show a poorer performance when applied in normal clinical practice [12 – 14]. This is likely for a variety of reasons, including low tidal volume ventilation, spontaneous respirations, arrhythmias, and heart valve regurgitation [12 – 14]. However, two other haemodynamic factors which can compromise predictive ability require consideration. First, standardized volumes (e.g. 10 ml/kg) of administered fluid may not produce equivalent alterations in preload between patients. This is due to variability in: (a) baseline blood volume, (b) mechanics of the venous vasculature (capacitance, compliance and resistance), (c) transthoracic pressure gradients, and (d) myocardial diastolic function [15, 16]. Second, patients with diminished contractility will manifest a flatter gradient of the Frank-Starling curve, yielding smaller changes in stroke volume for a given change in preload [17, 18].

Prediction of fluid responsiveness remains relatively under-explored in the paediatric intensive care unit (PICU), perhaps due to the challenges of cardiac output measurement. To date, most studies are small (typically <50 patients), and thus potentially both underpowered and prone to type 1 error [5]. None, to our knowledge, have addressed the two haemodynamic factors alluded to above. Thus, we aimed to evaluate volume responsiveness in a large PICU cohort (n = 100), using an accurate, indicator dilution method for cardiac output measurement. Our aims were three fold:

(i) to evaluate the predictive ability (stroke volume increase >15% after fluid administration) of a range of static and dynamic variables derived using two commercially available devices;

(ii) to document typical changes in volumetric variables after a constant fluid bolus (10 ml/kg), and investigate factors associated with change in preload (end diastolic volume);

(iii) to investigate whether the baseline myocardial contractile status influences stroke volume response and hence predictive ability.

6.3 Methods

This prospective, non-randomized study was conducted within a 20-bed multi-disciplinary PICU, after ethics committee approval and parental informed consent. Detailed methodology is available in the electronic supplement. Briefly, haemodynamic measurements were made within 24 hours of admission, timed to coincide with fluid bolus administration. Fluid boluses (typically 0.9% saline or Hartmann's solution at 10ml/kg of crystalloid over 20 minutes), were administered at the attending clinicians' discretion, who were blinded to the advanced haemodynamic measurements. Variables were measured less than 15 minutes before, and up to 30 minutes after fluid administration.

Standard haemodynamic variables included heart rate, arterial and central venous pressures. Advanced haemodynamic variables (table 1) were measured using two commercially available devices. The first, CO-Status™ (Transonic systems, Ithaca, NY), uses an indicator dilution method: transpulmonary ultrasound velocity.[19] A central venous injection of 0.9% saline (0.5 -

1ml/kg, max 20ml) is given, and blood is pumped through the arterial limb of an extra-corporeal arterio-venous loop. The principle involves saline diluting the blood in proportion to total blood flow (cardiac output), resulting in a similar proportionate change in transit time, and hence velocity, of an ultrasound beam passed across the arterial loop. From this, an ultrasound dilution curve is produced, and cardiac output calculated via the Stewart-Hamilton equation. In addition, several static volumetric variables are calculated from the curve properties (table 1 and online supplement).[20]

The second device, Mostcare® (Vytech®, Padova, Italy) is a continuous system utilizing arterial pulse contour analysis (Pressure Recording Analytical Method, PRAM).[21] This technology calculates beat-to-beat stroke volume via a custom algorithm, as well as a range of dynamic variables (table 6-1). Variability measures (e.g. pulse pressure variability) were averaged over 30 seconds.

A positive fluid response was described as an increase in stroke volume index (SVI) $\geq$15% after fluid bolus. We chose arterial dp/dt_{MAX} as a measure of systemic ventricular contractility myocardial contractility, as this has correlates closely with intraventricular $dp/dt_{MAX.}$[22] Arterial load was as expressed as effective arterial elastance, using the Segers formula.[23] Cardiac volumetric data were allometrically scaled to body surface area using a power of 1.38 (i.e. $(m^2)^{1.38} = m^{2.6}$); hence volumes are expressed as $ml/m^{2.6}$. [24, 25]

Inclusion criteria were: (i) weight $\geq$2kg, (ii) age $\leq$16 years, (iii) pre-existing arterial and central venous lines. Exclusion criteria were: (i) significant valvular regurgitation, (ii) large anatomical shunts, (iii) residual left sided obstructive lesions (e.g. aortic stenosis, coarctation), (iv) extreme haemodynamic instability, (v) arrhythmias. Exclusions (i) to (iii) were screened using transthoracic echocardiography. Patients with repaired single ventricle physiology (i.e. post Fontan operation) were included, as this should not compromise indicator dilution based cardiac output assessment. However, the effect on intravascular volume estimation (which relies on mean transit times) is unknown: thus a sensitivity analysis was anticipated (with and without Fontan patients).

Table 6-1 Advanced haemodynamic variables measured

Advanced Haemodynamic Variables	Abbreviation	Units	Modality	Definition
Stroke Volume Index	SVI	ml / $m^{2.6}$	TPUD	Volume of blood ejected from the heart during a single cardiac cycle
Cardiac Index	CI	L / min / $m^{2.6}$	TPUD	Volume of blood ejected from the heart per minute
Systemic Vascular Resistance Index	SVRI	Dyne-sec / cm^5 / $m^{2.6}$	TPUD	Mean arterial – central venous pressure x 80 / cardiac index
Effective Arterial Elastance	EAE	mmHg / ml / $m^{2.6}$	TPUD	Composite measure of arterial load, based on a 2-element Windkessel model that includes peripheral resistance and total arterial compliance
Static Variables				
Total End Diastolic Volume Index	TEDVI	ml / $m^{2.6}$	TPUD	Sum of end-diastolic volumes of the atria and ventricles
Central Blood Volume Index	CBVI	ml / kg	TPUD	Volume of blood between the injection (central vein) and recording (artery) sites, which includes the volume of blood in the heart, lungs, and large vessels
Active Circulating Volume Index	ACVI	ml / kg	TPUD	Volume of blood in which the indicator (saline) mixes in one minute from the time of injection
Maximum rate of systolic arterial pressure rise	dp/dt_{MAX}	mmHg / sec	PRAM	Maximum rate of systolic arterial pressure rise
Dynamic Variables				
Systolic Pressure Variation	SPV	%	PRAM	Difference between the maximum and minimum systolic pressures divided by mean systolic pressure during one mechanical breath
Pulse Pressure Variation	PPV	%	PRAM	Difference between the maximum and minimum pulse pressures divided by mean pulse pressure during one mechanical breath
Stroke Volume Variation	SVV	%	PRAM	Difference between the maximum and minimum stroke volume divided by mean stroke volume during one mechanical breath

TPUD = transpulmonary ultrasound dilution; PRAM = pressure recording analytical method.

Statistical Methods

Data are expressed as mean (± SD), or median (IQR). Bivariate comparisons were via unpaired t-tests. Models evaluating factors predicting and explaining fluid response were constructed using multilevel logistic and linear regression respectively (adjusted for multiple measurements within patients). Model fit was quantified by the area under the receiver operating characteristic curve (AUC) for logistic models, and adjusted r^2 for linear. Collinearity was quantified via the Variance Inflation Factor. The statistical software was Stata v13.1 (StataCorp Texas).

6.4 Results

Study Population and Measurements

One hundred mechanically ventilated children, median (IQR) age 18 (6 - 48) months, and weight 10 (5.6 – 15) kg were enrolled between September 2010 and May 2012. The majority were admitted following cardiac surgery (electronic supplement table E2). Two subsets of this population have been published elsewhere [26, 27], and abstract results containing the first 47 patients are reported in a systematic review.[5]

A total of 169 paired (pre- and post-fluid) measurements were taken; no patient had > 5 measurement pairs. On review of the raw data from the dilution curves and PRAM outputs, 27 measurements were rejected due to poor signal quality or data capture issues, leaving 142 measurements for final analysis. Of these, 116 (82%) were taken while patients were receiving inotropic agents (predominantly milrinone), and 19 (13%) were receiving vasopressors. All patients were mechanically ventilated in SIMV mode (see table E3, online supplement). Muscle relaxants were not routinely used; however sedation level was titrated to minimise spontaneous respirations, as evidenced by concordance of the set SIMV and measured patient respiration rates (table E3, online supplement). None received renal replacement therapy. The overall response rate (SVI increase ≥15%) was 45.1% (64/142).

Prediction of fluid responsiveness

There were no significant differences in baseline, basic haemodynamic data between responders and non-responders (table 6-2). However responders demonstrated lower stroke volumes and cardiac indices and higher systemic vascular resistance and effective arterial elastance.

Responders had significantly different values than non-responders for all baseline static haemodynamic variables, but for none of the dynamic variables (table 6-2). Of relevance to the dynamic variables, there were no differences between the two groups in terms of expiratory tidal volumes: 12.0 $\pm$ 3.3 versus 11.8 $\pm$ 3.8 ml/kg ($p = 0.73$) or respiratory rate 18.4 $\pm$ 2.2 versus 18.6 $\pm$ 2.2 ($p = 0.69$).

Despite these statistical differences, overall prediction was poor, with static volumetric variables generally performing better than dynamic variables in terms of AUC (table 6-2). The highest predictive value was demonstrated for TEDVI (AUC 0.67), with optimal prediction occurring at TEDVI of 240 ml/$m^{2.6}$. This yielded: sensitivity of 45.3%, specificity of 85.9%, and a correct classification rate of 67.6%. Prediction improved significantly when dp/dt_{MAX} was added as a second predictor to TEDVI (AUC increased from 0.67 to 0.71, $p = 0.02$).

Table 6-2 Baseline haemodynamic variables according to fluid responsiveness

Haemodynamic Variable	Units	Response (N = 64)	Non-response (N = 78)	P	AUC (95% CI)
Basic					
Heart Rate (bpm)	bpm	141 (23)	135 (22)	0.10	_
Central venous pressure	mmHg	8.8 (3.7)	9.1 (3.5)	0.66	0.53 (0.43 to 0.63)
Systolic Blood Pressure	mmHg	93 (21)	87 (18)	0.07	_
Diastolic Blood pressure	mmHg	51 (11)	49 (10)	0.27	_
Advanced: Routine					
Stroke Volume Index	ml / $m^{2.6}$	28 (8)	34 (12)	0.001	_
Cardiac Index	L / min / $m^{2.6}$	3.9 (1.1)	4.5 (1.6)	0.01	_
Systemic Vascular Resistance Index	Dyne-sec / cm^5 / $m^{2.6}$	1267 (624)	1067 (456)	0.03	_
Effective Arterial Elastance	mmHg / ml / $m^{2.6}$	2.59 (1.1)	2.08 (0.89)	0.002	_
Advanced: Static					
Total End Diastolic Volume Index	ml / $m^{2.6}$	259 (75)	306 (82)	<0.001	0.67 (0.58 to 0.76)
Central Blood Volume Index	ml / kg	16.1 (3.6)	17.7 (5.1)	0.04	0.59 (0.49 to 0.68)
Active Circulating Volume Index	ml / kg	46.2 (11.8)	53.3 (15.5)	0.003	0.64 (0.55 to 0.73)
Maximum rate of systolic arterial pressure rise	mmHg / sec	1116 (392)	958 (346)	0.01	0.61 (0.52 to 0.70)
Advanced: Dynamic					
Systolic Pressure Variation	%	12.6 (8.6)	10.4 (6.8)	0.10	0.59 (0.50 to 0.69)
Pulse Pressure Variation	%	23.3 (11.2)	21.8 (9.4)	0.38	0.54 (0.44 to 0.64)
Stroke Volume Variation	%	22.9 (6.8)	23.3 (7.7)	0.79	0.53 (0.43 to 0.62)

Data are presented as mean (SD), and refer to paired measurement episodes (n = 142). AUC = area under receiver operating characteristic curve; bpm = beats per minute.

Factors associated with change in preload (total end diastolic volume)

Fluid bolus increased TEDVI, on average by 34.6 ± 34.2 ml/$m^{2.6}$ for responders, and 8.4 ± 34.7 ml/$m^{2.6}$ for non-responders ($p < 0.001$). There were similar inter-group differences for other volumetric variables: delta CBVI (2.2 ± 2.3 versus -0.11 ± 2.4 ml/kg, $p<0.001$), delta ACVI (6.3 ± 5.4 versus 0.4 ± 5.4 ml/kg, $p<0.001$). The correlation between delta TEDVI and delta CBVI was $r = 0.71$, $p<0.001$, which was higher than that for delta TEDVI and delta ACVI, $r = 0.42$, $p<0.001$. Delta TEDVI did not have a significant correlation with delta central venous pressure, $r = 0.14$, $p = 0.10$, nor delta heart rate, $r = 0.08$, $p = 0.37$. Also, there was no difference in heart rate change after volume between responders and non-responders (mean change -4.7 versus -3.2 beats per minute, $p = 0.24$).

There was a weak inverse relationship between delta TEDVI and baseline TEDVI ($r = -0.19$, $p = 0.02$, figure 6-1), but none between delta TEDVI and baseline central venous pressure ($r = -0.03$, $p = 0.72$), expiratory tidal volume ($r = -0.01$, $p = 0.89$), dp/dt_{MAX} ($r = 0.10$, $p = 0.24$) or arterial load ($r = -0.02$, $p = 0.83$, see supplement figure E1,).

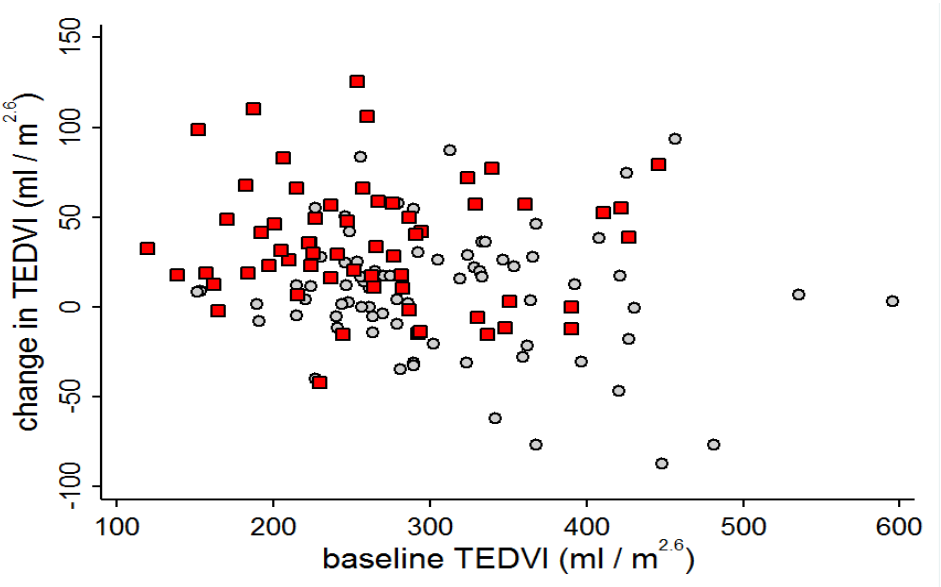

Figure 6-1 Scatterplot showing baseline versus change in total end diastolic volume after fluid administration. Gray circles represent patients who did not respond to fluid bolus, red squares represent responders. TEDVI; total end diastolic volume index.

Factors influencing fluid responsiveness

We investigated the joint influence of change in preload (delta TEDVI), baseline systemic ventricular contractility, and arterial load on the change in stroke volume (delta SVI) after fluid bolus using multivariable linear regression (table 6-3, figure 6-2). The model explained 45% of the variability in delta SVI after fluid bolus, with delta TEDVI being the dominant factor, exhibiting a partial R^2 value approximately 5 times greater than that for contractility (dp/dt_{MAX}). Of note, arterial load was not related to delta SVI.

Table 6-3 Regression model quantifying the relationship between haemodynamic factors and change in Stroke Volume Index after fluid bolus. The overall model R^2 was 0.45.

Haemodynamic Factor	Variable	Unit of measurement	Coefficient	95% CI	P	Partial R^2	VIF
Change in Preload	ΔTEDVI	per 10 ml / $m^{2.6}$	0.84	(0.67 to 1.01)	<0.001	0.40	1.02
Baseline contractility	dp / dt_{MAX}	per 100 mmHg / sec	0.31	(0.14 to 0.48)	<0.001	0.08	1.01
Arterial Load	EAE	per mmHg / ml / $m^{2.6}$	0.14	(-0.49 to 0.77)	0.66	0.001	1.01

CI = confidence interval; VIF = variance inflation factor.

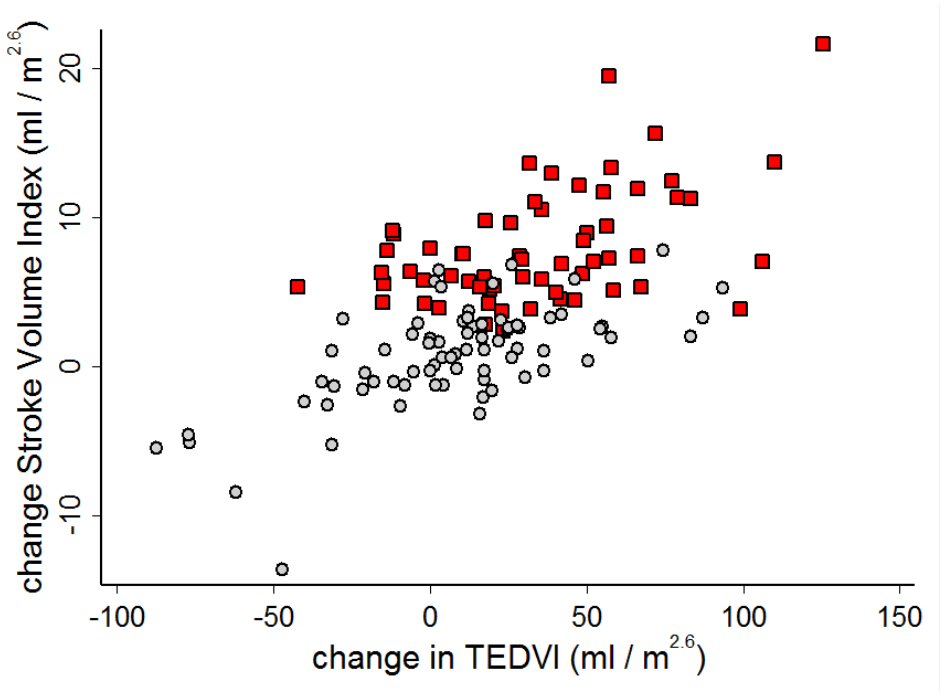

Figure 6-2 Scatter plot demonstrating the relationship between absolute change in stroke volume index and absolute change in total end diastolic volume index after fluid administration.TEDVI; total end diastolic volume index. Gray circles represent patients who did not respond to fluid bolus, red squares represent responders.

Although delta TEDVI explained the majority of the variability in delta SVI, baseline contractility was nonetheless an important factor. This is shown in figure 3, which was constructed using the regression coefficients from table 6-3. Here the gray horizontal bar represents the cut off whereby a positive delta SVI response is defined as $\geq$15%. Children with high baseline contractility, defined as a $dp/dt_{MAX} \geq 75^{th}$ centile ($\geq$1300 mmHg/sec), typically achieved a positive SVI response with delta TEDVI values of 10 to 15 $ml/m^{2.6}$, whereas patients with low contractility ($dp/dt_{MAX} \leq 25^{th}$ centile, $\leq$800 mmHg/sec), typically required delta TEDVI values of 35 to 40 $ml/m^{2.6}$.

Sensitivity Analyses

Analyses were repeated (n=114) after excluding single ventricle patients (post Fontan procedure). This produced a significant improvement in predictive ability for dp/dt_{MAX}, with AUROC increasing from 0.61 to 0.68 (see supplement table E4). For other variables, the

predictive ability changed only slightly, and not consistently. For example, the AUROC increased for TEDVI (from 0.67 to 0.69), but decreased for PPV (from 0.54 to 0.51). In terms of "Factors associated with change in preload" (see above), exclusion of Fontan patients did not produce major qualitative changes in the relationship between delta TEDVI and any variable. For "Factors influencing fluid responsiveness", Fontan exclusion improved regression model fit (R^2 increased from 0.45 to 0.53); however the coefficients and P values for individual variables changed little.

6.5 Discussion

Our first aim was to evaluate potential predictors of volume response using two novel, commercially available devices. Overall the predictive ability of most variables was poor, with static variables performing better than dynamic (see table 6-2). This is largely concordant with Gan's systematic review (12 studies, 438 children), which demonstrated limited predictive ability across a broader range of static and dynamic variables using different measuring devices to those in our study.[5] Our AUC values compared to Gan* are as follows: central venous pressure 0.53 versus 0.54, cardiac end-diastolic volumetric variables 0.67 versus 0.62, systolic pressure variability 0.59 versus 0.63, pulse pressure variability 0.54 versus 0.71, stroke volume variability 0.53 versus 0.69. The larger between-study AUC differences for the latter two variables have possible explanations. For pulse pressure variability, Gan's higher AUC is influenced by one outlier study; when this is excluded the value falls to 0.61 [5]. For stroke volume variability, our lower AUC may be due to different methods of calculation. We used PRAM, which was not assessed by Gan; this technology may provide an inaccurate paediatric estimate of stoke volume [26], and predicts volume response poorly in adult studies, yielding an AUC of 0.60.[28]

It is interesting to note that the predictive ability for the dynamic, arterial waveform-derived variables is markedly lower in children compared to adults, where typical AUROC values range

* Calculated using pooled, weighted data from relevant studies within Gan [5]

from 0.84 to 0.96 [29, 30]. This may be due to age-related differences in vascular mechanical properties, affecting arterial waveform behaviour. There are dramatic (at least two-fold) changes in both total arterial compliance and aortic characteristic impedance (normalized to body surface area) from birth to adulthood [31, 32], associated with changes in arterial vessel wall thickness and collagen fibre quantity/length [33]. There are also inherent differences in vascular properties within paediatric pathologies. For example, in congenital cardiovascular disease, average arterial elastance may exhibit two-fold differences, dependent upon the anatomic cardiac lesion, being both higher and lower than that for normal children [34].

However, these arterial mechanical factors would likely only explain a proportion of the differences between paediatric and adult studies. Thus, our second and third aims of our study involved investigating factors that may affect predictive ability. Unsurprisingly, the largest determinant of change in SVI with volume loading was change in preload, as measured by TEDVI. However, preload did not change in a consistent fashion after volume loading, with delta TEDVI being only weakly correlated with baseline TEDVI (figure 1). This relationship was three to four times weaker in our patients compared to adults with sepsis [35], and in an animal hemorrhagic model [36], yielding correlation coefficients of -0.19 (current study), versus -0.65 and -0.73, respectively. We do not know the reason for this, but speculate that it may be due to variable degrees of systemic inflammation and capillary leak, differences in diastolic function [37, 38] and venous mechanics [39, 40] in paediatrics. Of note, very little is known about the mechanics of venous return in paediatric critical illness.[41]

Our third finding emphasized the importance of considering systemic ventricular contractility when assessing predictive ability of end diastolic volume. Although highlighted by others, this has only been quantified in terms of change in AUC when contractility is dichotomized as “poor” versus “preserved”.[42, 43] We have extended these findings, by considering contractility as a continuous variable (table 6-3, figure 6-3), allowing for a more precise quantification. This shows that a patient with poor baseline contractility needs an absolute increase in end diastolic volume approximately 3 to 4 times greater than a patient with good contractility (i.e. 35 to 40 ml/$m^{2.6}$ versus 10 to 15 ml/$m^{2.6}$) to achieve SVI “responder” status (i.e. SVI increment $\geq$15%). This obviously requires higher volumes of fluid loading: Reuter showed, that critically ill adult patients

with reduced contractility require, on average 25 ml/kg of 6% hetastarch to reach the top of their Starling curves.[18] The clinical implications of this are important for patients with reduced contractility, who will require increased volume administration if a stroke volume increase >15% is targeted, but are also at higher risk of inadequate fluid clearance and hence fluid overload.[44] Earlier inotrope usage with judicious fluid administration may be a preferable strategy for such patients.

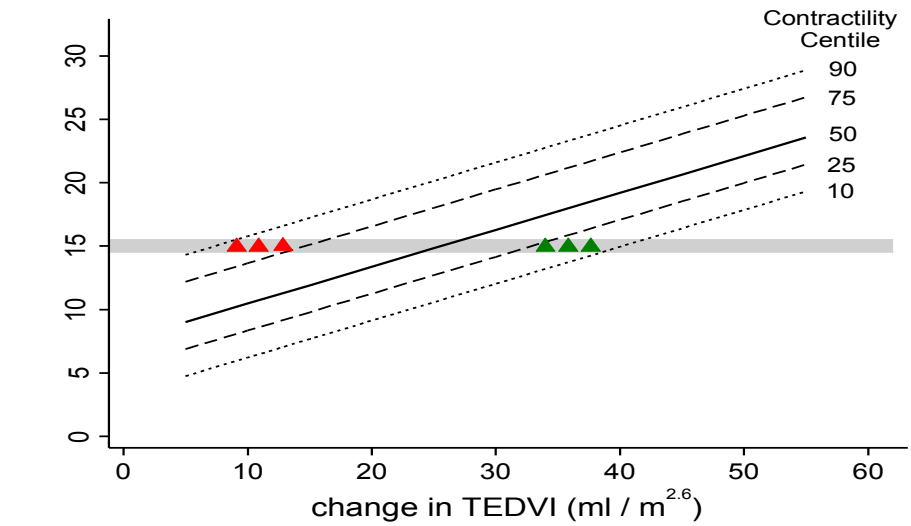

Figure 6-3 Regression derived multivariable relationship between percentage change in stroke volume index and absolute change in total end diastolic volume index after fluid administration, taking into account baseline contractile state.. Isobars represent centiles of contractility (dp/dt_{MAX}) for the study population. The gray horizontal bar represents the cut off when a positive delta Stroke Volume Index response is defined as ≥15%.Red solid triangles represent patients with good base line contractility whereas green solid triangles represent children with poor contractility. TEDVI; total end diastolic volume index

Study Limitations

1) SVI and the volumetric variables (TEDVI, ACVI and CBVI) were derived from aspects of the ultrasound dilution curve, raising the possibility of mathematical coupling. Reassuringly however, several clinical and animal studies have shown that coupling is unlikely with transpulmonary dilution curves, as volumetric variables remained constant when stroke volume was altered with beta agonists/blockers [35, 45, 46].

2) We may not have evaluated stoke volume variability accurately, as PRAM has been found to be an inaccurate measure of SVI [26]. This may explain the discrepancy between our findings and the good prediction (AUROC 0.85) for aortic peak velocity, a variable closely related to stroke volume variability [47]. However there is no reason to believe a similar error is present with PPV or SPV, as these were calculated directly from the arterial line.

3) Spontaneous ventilation can compromise the predictive value of dynamic variables. Although our patients were ventilated in SIMV mode, the concordance of the set SIMV and measured patient respiration rates (table E3), suggests that very little spontaneous respiration was occurring. Also, our AUROC for the dynamic variables were similar to other paediatric studies using CMV (see paragraph 1 of Discussion).

4) We used only one indirect measure of contractility (dp/dt_{MAX}), derived from the arterial, rather than the left ventricular waveform. However, this correlates closely with invasively measured intraventricular dp/dt_{MAX} in children [22]. Also, the PRAM estimate of dp/dt_{MAX} appears valid (despite being inaccurate for SVI) when compared to echocardiographically-derived dp/dt_{MAX} in adults [48]. It also tracks changes in inotropic state accurately in adults [49]. A limitation of this measure is its sensitivity to changes in preload [49]. However, this potential collinearity did not appear to be significant in our study, given the low regression variance inflation factors (table 3).

5) We did not assess the influence of venous mechanics on TEDVI response to volume loading. Bedside techniques for this are still relatively novel in adult practice [50], and pose distinct challenges in terms of paediatric application.

6) Clinical indications for fluid administration were not recorded. The likelihood of volume response may possibly differ, according to clinical indication or perhaps clinician seniority. Interestingly, a recent multicentre study has highlighted enormous variability with fluid challenges, in terms of indication, type, volume and assessment of response [51].

We suggest that these limitations are unlikely to change the three fundamental findings of our study. First, haemodynamic variables predict response to volume poorly, when SVI response is dichotomized as </≥15%. Second, that volume loading does not produce consistent changes in ventricular end diastolic volumes. Third, that baseline contractility plays an important role in influencing volume response. Paediatric studies investigating the role of venous mechanics in volume response are needed. We also suggest that more information would be gained from future studies if SVI response is expressed as a continuous variable.

Acknowledgments, Funding and Conflict of Interest:

The manufacturers of the advanced haemodynamic monitors used in this study (Transonic Systems, Ithaca, New York and Vytech, Padova, Italy) provided hardware and consumables free of charge. Rohit Saxena received an educational grant from Transonic Systems, Ithaca, NY to partially cover his student fees with Kings College London. The current work forms part of his submission for the research degree MD res (Doctor of Medicine: Research).

No Conflicts of Interest are declared for any author

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Chapter 6 Predicting fluid responsiveness in 100 critically ill children: the effect of baseline contractility - Online Data Supplement

Study Protocol

This prospective, non-randomized study was conducted within a 20-bed multi-disciplinary PICU, after approval by the regional ethics committee. Informed consent was obtained from all participants' parents.

Inclusion criteria were: (i) weight >2kg, (ii) age <16 years and (iii) pre-existing arterial and central venous lines. Exclusion criteria were: (i) known significant valvular regurgitation, (ii) large anatomical shunts, (iii) residual left sided obstructive lesions (e.g. aortic stenosis, coarctation), (iv) extreme haemodynamic instability, and (v) arrhythmias. Exclusions (i) to (iii) were screened using transthoracic echocardiography. Extreme haemodynamic instability was defined as either of the following occurring in the 30 minute period before advanced haemodynamic variables were measured (see below): (a) ongoing fluctuations in the bedside haemodynamic variables of heart rate and/or blood pressure and/or central venous pressure greater than approximately 20% of baseline, or (b) requirement for an increase in inotropic or vasopressor support, greater than an increment of 5 mcg/kg/min for dopamine or 0.05 mcg/kg min for adrenaline or noradrenaline.

Standard hemodynamic variables included heart rate, arterial and central venous pressures. ECGs were checked to verify sinus rhythm. Arterial lines were age appropriate (the smallest was 22 gauge), and located in: femoral (n = 90), radial (n = 46), axilla (n = 4) and brachial (n = 2) sites. Invasive arterial pressure measurements were transduced via a standard disposable pressure transducer (Edwards Life Sciences, Irvine, CA, USA) and a dual output electronic module (Agilent, Technologies, Germany). One output is fed into the standard bedside monitor (IntelliVue MP70, Philips Healthcare, The Netherlands); while the other is connected to an arterial pulse contour monitor (see PRAM, below). All the arterial pressure tracings were zeroed before each measurement, and checked to exclude artifact.

Advanced hemodynamic variables (see main manuscript, table 1) were measured using two commercially available devices. The first, CO-StatusTM (Transonic systems, Ithaca, NY), uses an indicator dilution method: transpulmonary ultrasound dilution (TPUD)[1]. A central venous

injection of 0.9% saline (0.5 - 1ml/kg, max 20ml) is given, and blood is pumped through the arterial limb of an extra-corporeal arterio-venous loop. The principle involves saline diluting the blood in proportion to total blood flow (cardiac output), resulting in a similar proportionate change in transit time, and hence velocity, of an ultrasound beam passed across the arterial loop. From this, an ultrasound dilution curve is produced, and cardiac output calculated via the Stewart-Hamilton equation. In addition, several static volumetric variables are calculated from the curve properties (main manuscript, table 1).[2]

The second device, Mostcare® (Vytech®, Padova, Italy) is a continuous system utilizing arterial pulse contour analysis (Pressure Recording Analytical Method, PRAM).[3] This technology calculates beat-to-beat stroke volume via a custom algorithm, as well as a range of dynamic variables (main manuscript, table 1). Variability measures (e.g. pulse pressure variability) were averaged over 30 seconds.

Advanced hemodynamic measurements were made as soon as possible after patients were admitted to the PICU, timed to coincide with fluid bolus administration (all within 24 hours of admission). Baseline demographic and physiological data were collected at the same time. Fluid boluses (typically 0.9% saline or Hartmann's solution at 10ml/kg over 20 minutes), were administered at the attending clinicians' discretion, who were blinded to the advanced hemodynamic measurements. Variables were measured less than 15 minutes before, and up to 30 minutes after fluid administration. The sequence of advanced hemodynamic measurements is shown in figure 4-1,.

Paired TPUD and PRAM measurements were made as follows: Two consecutive TPUD measurements were made, and the dilution curves inspected. If the shape of the injection or dilution curves were unsatisfactory, or if the variation between the two measurements was greater than 20%, a third measurement was obtained. The readings were than averaged. This process typically took 3-5 minutes. PRAM measurements could not be obtained exactly at the same time, as the TPUD measurements required interruption of the arterial line. Thus, we averaged the continuous variables (systolic and pulse pressure variation, stroke volume variation and dp/dt_{MAX}) from PRAM for 3 minutes before and after the time corresponding to the

UD measurements. Thus, a complete set of comparative measurements took approximately 10 minutes. Heart rate was monitored continuously and non invasive blood pressure measurement performed every minute to ensure hemodynamic stability during this 10 minute period. We performed repeated comparisons (as above) after fluid bolus administration.

The coefficients of variation for the dilution curve-based measures are given in table E1

Table E1 Coefficient of variation for transpulmonary ultrasound dilution based measures

Hemodynamic Variables	Abbreviation	Units	Timing	Mean (SD) coefficient of variation
Stroke Volume Index	SVI	ml / $m^{2.6}$	pre volume	5.3 (5.1)%
			post volume	4.7 (4.0)%
Total End Diastolic Volume Index	TEDVI	ml / $m^{2.6}$	pre volume	5.3 (5.9)%
			post volume	4.6 (4.4)%
Central Blood Volume Index	CBVI	ml / kg	pre volume	4.6 (4.9)%
			post volume	4.4 (4.1)%
Active Circulating Volume Index	ACVI	ml / kg	pre volume	7.5 (6.9)%
			post volume	7.8 (6.7)%

A positive fluid response was described as an increase in stroke volume index (SVI) $\geq$15% after fluid bolus. We chose arterial dp/dt_{MAX} as a measure of myocardial contractility, as this has correlates closely with intraventricular dp/dt_{MAX} .[4] Arterial load was as expressed as effective arterial elastance, using the formula of Segers.[5] Cardiac volumetric data were allometrically scaled to body surface area using a power of 1.38 (i.e. $(m^2)^{1.38} = m^{2.6}$); hence volumes are expressed as $ml/m^{2.6}$.[6, 7]

Table E2 Patient population by diagnostic reason for admission

Diagnosis		N
Post Cardiac Surgery*		90
- Ventricular septal defect repair	*(n = 17)*	
- Total cavopulmonary connection	*(n = 17)*	
- Tetralogy of Fallot	*(n = 10)*	
- Atrioventricular septal defect	*(n = 9)*	
- Total anomalous pulmonary venous drainage	*(n = 7)*	
-Aortic coarctation / hypoplastic aortic arch	*(n = 5)*	
- Other cardiac anomaly	*(n = 25)*	
Sepsis		8
Respiratory Illness		2
Total		100

* For cardiac surgical patients, the median (IQR) times for cardiopulmonary bypass and aortic cross clamp were 80 (53 to 105) and 53 (35 to 74), respectively.

Table E3 Mechanical ventilatory variables

Respiratory Variable	Units	Value
FIO_2	%	38 (12.4)
Peak Inspiratory Pressure	cm H_2O	19.9 (3.1)
Positive End Expiratory Pressure	cm H_2O	5.2 (1.5)
Mean Airway Pressure	cm H_2O	8.9 (1.9)
SIMV rate	resp / min	18.5 (2.2)
Measured Patient Rate	resp / min	18.4 (2.8)
Expiratory Tidal Volume	ml /kg	11.9 (3.6)
Oxygen saturations	%	97.8 (4.8)

Data are presented as mean (SD), and refer to values taken before paired measurement episodes (n = 142).

Table E4 Baseline hemodynamic variables according to fluid responsiveness, with Fontan (single ventricle) patients excluded

Hemodynamic Variable	Units	Response (N = 52)	Non-response (N = 52)	P	AUC (95% CI)
Basic					
Heart Rate (bpm)	bpm	142 (25)	135 (24)	0.13	_
Central venous pressure	mmHg	7.8 (2.8)	8.2 (2.9)	0.54	0.54 (0.43 to 0.64)
Systolic Blood Pressure	mmHg	94 (22)	87 (19)	0.08	_
Diastolic Blood pressure	mmHg	52 (12)	50 (10)	0.41	_
Advanced: Routine					
Stroke Volume Index	ml / $m^{2.6}$	28 (8)	33 (12)	0.008	_
Cardiac Index	L / min / $m^{2.6}$	3.9 (1.1)	4.4 (1.6)	0.05	_
Systemic Vascular Resistance Index	Dyne-sec / cm^5 / $m^{2.6}$	1338 (654)	1128 (466)	0.05	_
Effective Arterial Elastance	mmHg / ml / $m^{2.6}$	2.71 (1.1)	2.17 (0.90)	0.005	_
Advanced: Static					
Total End Diastolic Volume Index	ml / $m^{2.6}$	256 (76)	308 (84)	<0.001	0.69 (0.59 to 0.79)
Central Blood Volume Index	ml / kg	16.3 (3.6)	17.9 (5.1)	0.06	0.58 (0.47 to 0.68)
Active Circulating Volume Index	ml / kg	47.3 (12.5)	55.3 (15.7)	0.004	0.65 (0.55 to 0.76)
Maximum rate of systolic arterial pressure rise	mmHg / sec	1111 (408)	861 (274)	<0.001	0.68 (0.58 to 0.78)
Advanced: Dynamic					
Systolic Pressure Variation	%	12.1 (9.4)	10.3 (7.4)	0.25	0.58 (0.47 to 0.68)
Pulse Pressure Variation	%	21.4 (9.8)	21.9 (9.8)	0.79	0.51 (0.40 to 0.61)
Stroke Volume Variation	%	22.0 (6.6)	23.2 (8.3)	0.39	0.55 (0.45 to 0.66)

Data are presented as mean (SD), and refer to paired measurement episodes (n = 114). Abbreviations: AUC, area under receiver operating characteristic curve; bpm, beats per minute.

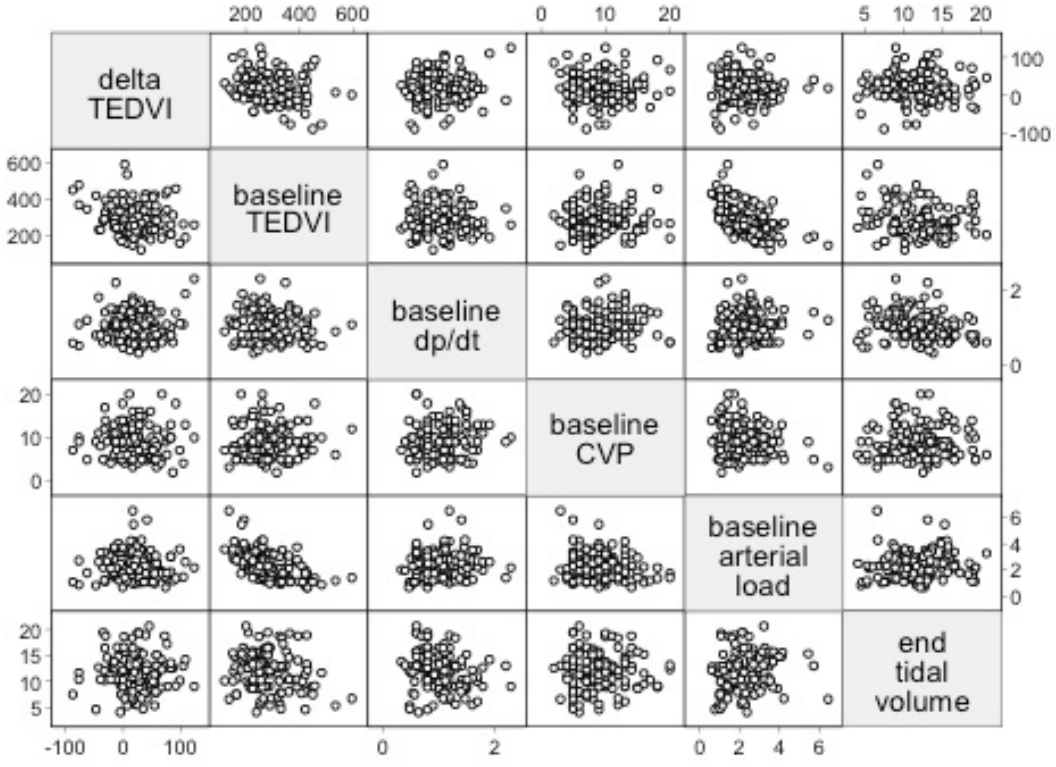

Figure E1. Pairwise scatter plots showing relationships between selected baseline haemodynamic variables and change (delta) in total end diastolic volume after volume administration.
Abbreviations: TEDVI = total end diastolic volume index; dp/dt = maximum rate of systolic arterial pressure rise; CVP = central venous pressure.

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Chapter 7 Accuracy of transpulmonary ultrasound dilution method for detection of small anatomic shunts.

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7.1 Abstract

Purpose

To investigate the qualitative and quantitative accuracy of transpulmonary ultrasound dilution (TPUD) (COstatus™, Transonic Systems) for the detection of small anatomic shunts.

Methods

Prospective, observational study in a multi-disciplinary paediatric intensive care unit. Seventy three critically ill children (67 post cardiac surgery), with a median (IQR) age of 10 (3-50.3) months and a median (IQR) weight of 8 (3.43-13) kg were enrolled.

Measurements: Ultrasound dilution (TPUD) measurements were performed on patients within one hour of undergoing two-dimensional echocardiography, which was used as the comparator technique. Shunt was diagnosed by characteristic changes on the TPUD curve shape, and was considered “test-positive” only if two or more measurements suggested the presence of the shunt. The TPUD technology also provided an estimate of systemic to pulmonary blood flow ratio (Qp:Qs).

Results

12/73 (16.4%) patients had a shunt identified by both TPUD and echocardiography. The overall accuracy (95% Conf. intv.) was 86.1% (75.6 to 96.6%), with a sensitivity of 85.7% (57.2 to 98.2%) and specificity of 86.4% (75.0 to 94.0%). The estimated Qp:Qs ranged from 0.7 to 1.4, which was consistent qualitatively with the echocardiographic findings on colour flow Doppler. Shunt was detected by TPUD alone in 8 children; 6 of these had clinical conditions known to compromise dilution curve analysis (valve regurgitation, asymmetric pulmonary blood flow). Shunt was detected by echocardiography alone in 2 children; in both cases the shunt was tiny.

Conclusions

TPUD is an accurate method for the detection of small anatomical shunts, both qualitatively and quantitatively.

Key Words

Ultrasound dilution, Echocardiography, Shunt detection.

7.2 Introduction

Critically ill children admitted to the paediatric intensive care unit (PICU) may have undiagnosed anatomic shunts, both cardiac and extra cardiac in origin. This phenomenon has been investigated predominantly following corrective cardiac surgery for congenital heart disease, where the incidence of echocardiographically diagnosed residual shunt may be in the range of 33 – 38% for certain lesions.[1-4] However, the accuracy of shunt identification may vary according to the timing of imaging (relative to surgery), and the echocardiographic modality used.[3] Anatomic shunting may also be common among patients without known cardiac disease, who are admitted to the general intensive care unit for other reasons. For example, patent foramen ovale is a common lesion in the general population, occurring in approximately 30% of adults.[5] The potential for this to result in hypoxemia from right to left shunting increases in the PICU setting, where elevated right sided pressures may occur secondary to pulmonary disease. Accurate and prompt diagnosis of anatomic shunts may be further hampered by lack of an on-site cardiology service, which may lead to increased morbidity and prolonged length of stay. Thus, an accurate alternative method for diagnosing anatomic shunts would be beneficial.

Transpulmonary ultrasound dilution (TPUD) (COstatus® Transonic systems, Ithaca, NY, USA) is a novel, invasive technology [6] capable of accurately measuring cardiac output and blood volumes in small children [7], paediatric animal models [8,9] and adults.[10,11] In addition to hemodynamic volumetric assessment, TPUD technology can detect the presence of anatomical shunts based upon the shape of the dilution curves. This method utilizes pre-existing central venous and arterial lines, and does not require special skills apart from the correct indicator injection technique. Catheter laboratory studies in children [12] and an animal model [13] showed high sensitivity and specificity of this technology for the identification of large shunts. Recently, Lindberg et al [14] reported TPUD to be an accurate tool for shunt detection when compared with transoesophageal echocardiography in the immediate post operative cardiac surgery period in 21 children. In addition, they demonstrated no significant difference between the TPUD technology and transit time ultrasound flow probes (considered as gold standard for flow measurements) for the measurement of Qp:QS (ratio between pulmonary to systemic blood

flow) preoperatively in the same cohort of patients. However, both the paediatric studies mentioned above [12,14] typically investigated subjects with left to right shunts only.

We carried out our study with the aim to evaluate the TPUD method for (a) the accuracy of detection of small anatomic shunts and (b) the assessment of right to left and bidirectional shunts in addition to the left to right shunts (Qp:Qs estimation) in a cohort of critically ill children.

7.3 Material and Methods

This was a prospective, single centre, observational study conducted within a 20 bed multi-disciplinary PICU between September 2010 to August 2012. The study was approved by the regional ethics committee (South East London REC2, 10/H0802/62). Written informed consent was obtained from all the parents or the legal guardians.

7.3.1 Study subjects

The children included in this study were part of a larger 100 patient cohort of critically ill children enrolled for studying their hemodynamic profiles.[15] Seventy-three children (45 males) with the median (IQR) age and weight of 10 (3 - 50.3) months and 8 (3.43 - 13) kg respectively, were included into this study. Sixty seven (91.8%) were post cardiovascular surgery, 5 (6.8%) had an admission diagnosis of sepsis and 1 child (1.4%) had primary respiratory pathology The remaining twenty seven children were excluded from the analysis as they fell into one of the categories of the exclusion criteria (see below). All 73 subjects had pre-existing central venous and arterial catheters (see inclusion criteria below). Sixty eight (93.2%) patients had central venous catheter in the superior vena cava, placed percutaneously via the internal jugular approach, with the remainder sited in the inferior vena cava, via the femoral vein. Catheter position was confirmed radiographically.

7.3.2 Inclusion and exclusion criteria

Children admitted to the PICU with pre-existing arterial line, central venous access and a clinical indication for echocardiography were considered for study inclusion. Clinical indications for echocardiography included (a) routine post cardiac surgery imaging, or (b) requirement for significant haemodynamic support (>60ml/kg fluid resuscitation in the previous 24 hours, or the need for dopamine infusion > 5mcg/kg/min) or (c) presence of a murmur.

Exclusion criteria included children with: (a) extreme hemodynamic instability, (b) previously recognized valvular regurgitation, (c) known unrepaired anatomical shunts and (d) single ventricle physiology. Extreme haemodynamic instability was defined as either of the following occurring in the 30 minute period before transpulmonary ultrasound dilution measurement and echocardiography: (a) ongoing fluctuations in the bedside haemodynamic variables of heart rate and/or blood pressure and/or central venous pressure greater than approximately 20% of baseline, or (b) requirement for an increase in inotropic or vasopressor support, greater than an increment of 5 mcg/kg/min for dopamine or 0.05 mcg/kg min for adrenaline or noradrenaline.

7.3.3 Data collection

The following data were collected within the first 24 hours following admission to the PICU: (a) ultrasound dilution measurements (b) 2D echocardiography (c) demographics and (d) hemodynamic data.

7.3.4 Transpulmonary Ultrasound Dilution measurements

The transpulmonary TPUD technique utilizes an extra-corporeal arterio-venous (AV) loop and two reusable ultrasound sensors - one on each side of the loop [6]. A roller pump provides a constant blood flow rate 9-12 ml/min in the AV loop. Normal saline (0.5 – 1 ml/kg, maximum

30ml) at body temperature is used as an indicator, and injected via the venous limb. The velocity of an ultrasound beam directed through a column of isotonic saline at body temperature is 1533 m/sec which is different from that of blood (ranging typically between 1570 – 1585 m/sec). Thus, saline injected into the venous limb will produce a transient change in ultrasound velocity in both the venous and arterial limbs, in proportion to the degree of dilution. This is expressed graphically on the monitor as an arterial dilution curve (marked 'b' in Fig.3-2), with the y axis representing percent saline concentration in the arterial blood, and the x axis being time). The venous curve (marked as 'a' in Fig.3-2) on the screen only shows the shape of injection (flow) and is not normalized to percent dilution. The arterial dilution curve can be used to calculate cardiac output.

Dilution curves representing right to left shunts (see Fig. 3-4) exhibit a short appearance time (arrow 'a' on figure 3-4) and an abnormal upslope (arrow b) or an extra hump (arrow c). This is due to a part of the indicator bypassing the lungs through the shunt and reaching the arterial sensor earlier followed by the rest of the indicator.[16] Dilution curves representing left to right shunts (see Fig. 3-5) have a normal appearance time but there is more asymmetry of the downslope versus upslope than in normal curves, due to recirculation of the indicator (shown as 'd' in Fig.3-5). Bi-directional shunts demonstrated characteristic properties of both types of shunt i.e. short appearance times and asymmetry of the downslope.

Major dispersion of the dilution curve happens in the heart mixing chambers. The difference in the appearance time between femoral and radial artery locations is of the order of 2 cardio cycles. Location of the injection and the recording site is taken into account by the TPUD dilution software. The operator is required to enter these details before the measurement.

In addition to qualitative shunt detection, the software also provides a quantitative estimate of the ratio between the pulmonary to systemic blood flow (Qp/Qs). This is derived via algorithms based upon the observed changes in the shape of the dilution curve due to the presence of anatomical shunts.[16-18] Here, Qp/Qs is derived by comparing the predicted area under a normal dilution curve with the area of the observed dilution curve. In right to left shunts the observed area of the 'hump' represents part of the indicator that bypasses lungs. Thus, the ratio of the rest of the area (from indicator that passed the lungs) to the total area (including the 'hump') that

was recorded in the arterial site gives a Qp/Qs ratio less than one. In the case of left to right shunt, the observed area under the curve is larger than the area of the predicted normal dilution curve due to the presence of saline recirculation, resulting in an abnormally extended downslope. Thus the ratio of observed area under dilution curve to predicted area gives Qp/Qs ratio greater than one.

7.3.5 Procedure for validating shunt detection

Echocardiography was considered as the reference method for shunt detection. A single, detailed 2D echocardiographic scan was performed when clinically indicated. Transthoracic ultrasound examinations were performed using the Philips IE33 Ultrasound system (Philips Medical Systems, Andover, MASS, USA) using S12-4, S8-3 or S5-1 probe as appropriate for the patient size. Conventional echocardiographic methods were employed to detect residual shunts including cross-sectional echocardiography coupled with pulsed wave, continuous wave and colour flow Doppler assessment of any residual shunts. These techniques allow determination of whether the residual shunt is right to left, left to right or bidirectional but they cannot reliably quantify Qp:Qs in this setting. The operators commented on the direction of any residual shunt.

Shunt size was described as:

“tiny” if there was only a narrow jet of flow on colour flow Doppler which was not visualized on cross-sectional imaging alone,

“small” if the shunt jet appeared wider than 2mm and if a residual shunt could be visualized without colour flow Doppler.

“moderate to large”, where a shunt was not pressure restrictive and which appeared hemodynamically significant by volume loading of cardiac chambers.

Postoperative transthoracic echocardiographic imaging is often difficult due to the absence of good acoustic windows. If there were very small shunts detected by colour flow Doppler then occasionally the angle of insonation did not permit reliable measurement of jet direction, which typically occurs with very small colour flow Doppler jets. The final echocardiographic findings were agreed by two experienced observers (KN, JMS) who were blind to the TPUD results.

All TPUD measurements taken within one hour on either side of the echocardiogram were considered as eligible for shunt detection (fig 4-2). Ultrasound measurements were made for a variety of reasons. A minimum of one "set" of TPUD measurements was required as part of the study protocol; however we also performed additional sets of TPUD measurements when therapeutic manoeuvres were made for clinical indications within the time window (for example, administration of a fluid bolus or addition of a vasoactive agent). Each "set" of TPUD measurements required a minimum of two, sequential injections (each generating their own dilution curve). Significant abnormality in either the injection or dilution curves was detected by the CO Status® software. Measurements that had error messages such as: 'repeat: noisy base line', or 'make smooth short injection' lacked sufficient quality to be analysed for shunt by the software, and were excluded from the analysis. In such cases, injection was repeated until at least two analysable curves were produced. Ultrasound dilution was considered to have identified a shunt only if two or more measurements within a set suggested presence of the shunt. In all cases, operators performing both echocardiography and TPUD were blinded to the results from the other technique.

7.3.6 Statistical analysis

Diagnostic accuracy of the TPUD technique for shunt was quantified via calculation of sensitivity, specificity, accuracy and likelihood ratios (all were reported with 95% confidence intervals) using Stata v 12.1 (StataCorp, Texas, USA) incorporating the ado file "diagti" (courtesy of Aurelio Tobias and Paul Seed, downloaded from Stata Journal 4-4, sbe36_2)

7.4 Results

Paired TPUD and echocardiographic assessments were carried out in 73 children. Overall, 4.7% of TPUD measurements were not analysed by the software due to technical issues outlined above (see methods). We did not encounter thrombosis of the AV loop in any patient. Haemodynamic data at time of echocardiography and TPUD measurement, expressed as mean (SD), included: heart rate 137 (27) beats per minute, systolic blood pressure 92 (20) mmHg, diastolic blood pressure 51 (11) mmHg, and central venous pressure of 8.7 (3.7) mmHg. All patients were mechanically ventilated, and 65 (89%) required at least one agent for inotropic and/or pressor support. These included: milrinone (n = 64), dopamine (n = 20), adrenaline (n = 3), noradrenaline (n = 4) and levosimendan (n = 2). A set of TPUD dilution measurements was repeated for five children because of a therapeutic manoeuvre occurring within the time window between initial TPUD and echocardiography: four required fluid boluses (10 ml/kg) and two addition of an inotropic agent (one child requiring both). This did not affect shunt detection via TPUD, neither quantitatively nor qualitatively.

The prevalence of shunt by echocardiography was 19.2% (14/73). The qualitative diagnostic accuracy of TPUD for shunt detection is shown in the table. This gives a sensitivity (95% Conf. intv.) of 85.7% (57.2 to 98.2%), specificity of 86.4% (75.0 to 94.0%), accuracy of 86.1% (75.6 to 96.6%), positive likelihood ratio of 6.32 (3.21 to 12.5) ,and negative likelihood ratio of 0.17 (0.05 to 0.60). The positive and negative predictive values were 60% (36.1 to 80.9%) and 96.2% (87.0 to 99.5%) respectively.

Shunt was detected in 12 children by both TPUD and echocardiography (table). For 7 of these children, the direction of shunt flow by TPUD concurred with the echocardiographic assessment. In the remaining 5 children, the direction of the shunt by echocardiography was indeterminate due to the very small size of the shunt. However, TPUD designated a shunt direction in all 5 children (two each were left to right and right to left and one was bi-directional). In all five cases, the direction of shunt designated by TPUD was consistent with the anatomic lesion: both of the left to right shunts were seen following ventricular septal defect repair, the two right to left

shunts were seen following repair of tetralogy of Fallot and total anomalous pulmonary venous drainage (one each), and the bidirectional shunt occurred following atrioventricular septal defect repair with a small right ventricle.

Shunt was positive in eight children by TPUD only (seven of these were left to right and one was right to left), while 2 children had shunt detected by the echocardiography alone. Both shunts characterized by echocardiography alone were very small or tiny (see methods). Fifty one children had no shunt detected by either of the techniques.

Table 7-1 Concordance between TPUD and ECHO for detecting and excluding shunt

	Echocardiography positive (%)	**Echocardiography negative (%)**	**Total**
TPUD positive	12 (16.4%)	8 (11.0%)	20
TPUD negative	2 (2.7%)	51 (69.9%)	53
Total	14	59	73

The size of the TPUD-derived Qp:Qs ratio for those with left to right shunts was less than 1.4 in all cases. Similarly, the TPUD-derived Qp:Qs ratio for patients with right to left shunts was always greater than or equal to 0.8 (see Fig.7-1). All of these agreed with echocardiographic estimates, and constituted small or tiny shunts not requiring further surgical intervention. There was no difference in the mean (SD) values for TPUD-estimated Qp:Qs between shunts detected by both TPUD and echocardiography and those detected by TPUD alone: 1.13 (0.02) versus 1.15 (0.02) respectively, $p = 0.77$.

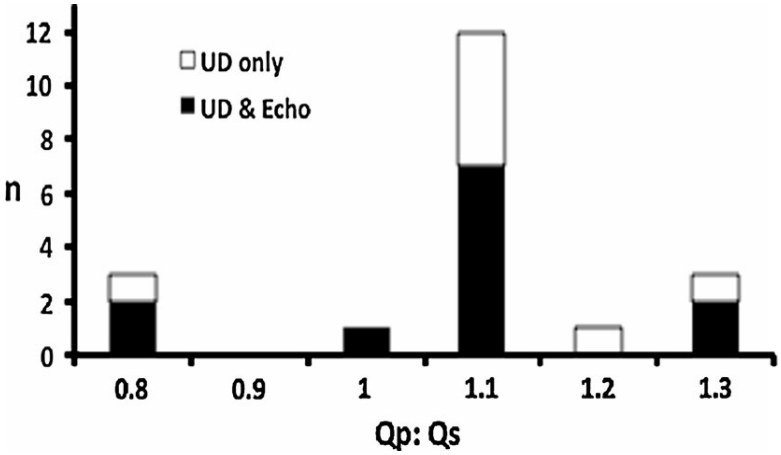

Figure 7-1 Distribution of pulmonary to systemic flow ratio estimated by TPUD. The size of the TPUD-derived Qp:Qs ratio for left to right shunts was less than 1.4 and for right to left shunts was always greater than or equal to 0.8. all cases.

7.5 Discussion

We have demonstrated broad agreement between TPUD and echocardiography in terms of both anatomical shunt detection (sensitivity 85.7%, specificity 86.4%) and quantification in a group of critically ill children with small residual shunts (Qp:Qs 0.83 to 1.34).

Utilization of dilution curves for the recognition and quantification of anatomic shunts is not new; studies using dye as the indicator first appeared in the mid 20th century.[19-22] To our knowledge, the largest study describing shunt detection via dye dilution was published by Morrow et al in 1966.[23] Dilution curves were recorded intra-operatively and postoperatively in 260 patients with pre-operative intra-cardiac shunts . Criteria for the shunt detection based upon dilution curves characteristics were analogous to ours. Their study demonstrated that, in 96 percent of the cases, the presence or absence of a shunt determined from the intraoperative curves was confirmed by the findings at the postoperative study, providing a reliable, objective assessment of the effectiveness of the surgical procedure via a minimally invasive approach. In the last decade, use of transpulmonary thermodilution for this purpose has been described, although only as isolated case reports.[24,25]

Boehne et al [12] compared TPUD with oximetry during routine cardiac catheterization in 20 children and adolescents with large shunts. They found a sensitivity of 100% and specificity of 92.8% for TPUD for identification of cardiac shunts as compared to the data from the cardiac catheterization. Shih et al [13] reported a success rate of greater than 95% for right to left shunt detection with a false positive rate of 3% and a false negative rate of 5.2% in an animal model using TPUD. However, subjects in both of these studies had large anatomical shunts which may have contributed to the high specificities and sensitivities.

Developments in TPUD indicator technology and curve analysis have provided two new potential advantages: (i) the ability to detect smaller shunts, and (ii) accurate quantification of the shunt direction and relative flow which has recently been substantiated by Lindberg et al.[14] They demonstrated no significant difference between the TPUD and the transit time ultrasound flow probes for the estimation of Qp/Qs in the pre-operative paediatric cardiac surgical children .This is potentially important for several reasons. First, shunt flow may be significant, even in relatively small shunts, and also out of proportion to pressure gradients across chambers connected by the shunt.[26,27] Second, intra- and extra-cardiac shunts are not always apparent on echocardiography[2,3,28,29] and may need confirmation and quantification via alternative investigational modalities such as MRI or cardiac catheterization, which carry different risk profiles for the patient. Thus, TPUD may be a useful screening tool to evaluate patients who may need more detailed investigation.

With this in mind, we have evaluated the performance of TPUD technology for detection and quantification of small shunts in a cohort of critically ill children. The sensitivity and specificity reported by us is slightly less than that reported in the above studies.[12,13] This may be due to four main reasons:

(a) Lack of a true gold standard for the reference method

The limitations of transthoracic echocardiography in the immediate post-operative period are well documented, where intra-cardiac shunt detection can be influenced by many factors

including the quality of windows post thoracotomy, type of operative repair and rapidly changing hemodynamics.[1-4] In addition, we did not investigate the false positive cases (shunt detected by TPUD only) for the presence of extra cardiac shunts, which are common with some cardiac lesions.[28,29] Overall, the net effect may be to inflate the apparent false positive rate.

(b) Timing of measurements

Our study design allowed for a two-hour window where TPUD measurements could be made (up to one hour either side of the echocardiogram), and included manoeuvres that could change shunt dynamics. However we chose this study design to reflect real world conditions, i.e. to mimic how TPUD may be used in everyday clinical practice.

(c) Size of the shunts

Shunt identification via an indicator dilution technique is influenced by the amount of indicator flow through the shunt, which is proportional to shunt size; hence larger shunts are generally associated with more abnormal curves. All the residual shunts identified by echocardiography in our cohort of children were very small or tiny as compared to those in the above studies, which may increase our false negative rate.

(d) Factors specific to left to right shunts

As previously discussed, asymmetry of the dilution curves produced from left to right shunting is proportional to the flow of indicator through the shunt, with most hemodynamically significant left to right shunts having a Qp/Qs ratio greater than or equal to 1.5. Asymmetry of the dilution curves may also occur in several clinical scenarios without shunting, as highlighted in the literature [16-22] and by the manufacturer. These include moderate or large valvular regurgitation, and substantial asymmetry of lung perfusion as seen after surgery for correction of total/partial anomalous pulmonary venous return or transposition of the great vessels. However, in these scenarios, the estimated Qp/Qs typically range between 1.1 and 1.4. Such conditions may have contributed to six of the eight false positive TPUD results in our study. Five of these children had

at least moderate valvular regurgitation and one child was post partial anomalous pulmonary venous return surgery. In all these cases the Qp/Qs values were between 1.1 and 1.4, well within the specification and thus not misleading the operator for presence of a large hemodynamically significant shunt.

Our results yielding a sensitivity and specificity of 85.7% and 86.4% respectively, demonstrate that TPUD represents an acceptable bedside tool for anatomical shunt detection. Given the potential confounding factors outlined above, it is possible that the accuracy is even higher. This compares favourably with intra operative transoesophageal echocardiography (an established method for detection of residual shunts), where a study of 573 post cardiac surgical patients yielded a sensitivity and specificity of 58% and 57% respectively versus transthoracic echocardiography.[1]

Furthermore, shunt quantification produced Qp:Qs estimates that were consistent with echocardiographic findings, in cases where a shunt was detected with both techniques.

A key limitation of our study (in addition to those outlined above) was a lack of larger shunts in our patient population. Although it is highly likely that TPUD will be accurate at detecting larger shunts, we do not yet know whether the quantitative estimates of QpQs in this setting are accurate; thus further studies using an accurate, quantitative comparator (for example, MRI) are required.

In addition to the above there are few limitations of the TPUD technology per se:

1) Use of an extra corporeal AV loop required heparinisation of the AV loop. However, the total amount of heparin required to flush the system was very small [Heparin concentration 1unit/ml; priming volume of the extra corporeal loop was 5.3 ml (2.7ml for the neonates)]. This was unlikely to have any significant effect on the coagulation profile of the patient. There was an option to redirect all the heparin solution into the injection syringe at the start of the measurement but this was not performed in our patients due to the small volume of heparin infused.

2) TPUD measurement required simultaneous use of both central venous catheter and arterial line. Invasive blood pressure monitoring was unavailable for the duration of the measurement (3-5min) . However, blood pressure was measured non invasively during the measurement period in these patients.

3) As the TPUD utilized normal saline (1ml/kg, maximum of 30 ml) as an indicator, recurring measurements can accumulate additional fluid which may be relevant in small babies and children.

7.6 Conclusion

The transpulmonary ultrasound dilution technique accurately diagnoses the presence of small anatomical cardiac shunts. The estimates of Qp/Qs agreed qualitatively with the echocardiographic assessment of observed shunts as tiny or small. The ability to provide Qp/Qs estimations may be beneficial in identifying the small shunt flow increasing to clinical significance.

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Chapter 8 Summary, Conclusion and Future direction

Advanced haemodynamic monitoring can prove beneficial for the management of critically ill children. This includes cardiac output monitoring and estimation of different markers for predicting fluid responsiveness in critically ill patients. CO monitoring could help physicians to differentiate between various causes of low blood pressure (such as low CO, low systemic vascular resistance index or both) . This could be useful in guiding and monitoring therapies intended for augmentation of CO (fluid bolus or inotrope administration). Previous studies have demonstrated inaccurate clinical estimation of CO hence, a range of devices is in use to measure CO. However, majority of them are intended and validated for use in adult patients. Their use in paediatric practice has been limited by technical challenges such as wide age and weight range, age variable vascular properties and rapidly changing haemodynamics with disease pathology.

We studied two different types of CO monitoring in children. TPUD is an indicator dilution based tool (normal saline is used as an indicator) requiring the use of an extra corporeal loop with each end connected to an existing arterial and central venous catheter. PRAM is a pulse contour based monitoring device, which is easily connected to an arterial catheter already present in many critically ill children.

Chapter 1 is a review of various commercially available methods for measuring cardiac output. There is a description of each method together with its advantages and limitations. The methods are also referenced to current literature review focussing on paediatric application and literature wherever possible. Though transpulmonary thermodilution technique is considered a gold standard for practical purposes but it is far from an ideal CO monitoring device. The current choice of any particular device is predominantly based upon clinician experience or preference, availability and patient factors. The chapter also introduces newer less invasive monitoring such as Nexfin and NICOM devices currently been investigated for clinical application.

Chapter 2 is a review of literature of the various static and dynamic markers, commonly employed in clinical practise for predicting fluid responsiveness. It discusses the physiological basis of origin of these markers including limitations of their use. Special emphasis is given to the static and dynamic markers measured by TPUD and PRAM respectively, along with the relevant literature review. We conclude (from literature review) that dynamic markers outperform static markers for prediction of fluid responsiveness in adult patients. Changes in the aortic blood flow peak velocity and passive leg raising showed consistent results. However, further studies are required to confirm their accuracy in paediatric practise.

Chapter 3 focuses on the physics and principles behind TPUD and PRAM. TPUD makes use of indicator dilution curves for calculation of CO based upon Stewart-Hamilton equation. In addition, it also measures three novel static markers - TEDVI, CBVI and ACVI. We investigated these markers for their utility in prediction of fluid responsiveness after fluid bolus administration or inotrope therapy. TPUD also provides qualitative and quantitative estimate for anatomic shunts based upon characteristics of dilution curves. PRAM on the other hand, is based upon pulse contour technology used with peripheral arterial catheters. It utilises arterial waveform characteristics to measure CO. In addition, it also measures dynamic markers - SPV, PPV and SVV, which were investigated for prediction of fluid responsiveness in our study. PRAM also gives an estimate of dP/dt max - a marker for systemic ventricular contractility. This enabled us to study the role of myocardial contractility in response to fluid bolus administration. We have also discussed the various limitations of these two methods.

Chapter 4 is a description of research methodology for different aspects of the study. The three main research questions investigated were (i) Validation of PRAM against TPUD (ii) Prediction of fluid responsiveness using static and dynamic markers including the effect of baseline contractility and (iii) Accuracy of TPUD for identification of small anatomic shunts.

Chapter 5 is a validation study for PRAM. PRAM is based upon pulse contour methodology but has not been validated for measuring CO in critically ill children. TPUD has recently been validated for the same cohort of children. This study investigated the accuracy of PRAM against TPUD technique. Our hypothesis for assessing the accuracy of PRAM for measuring absolute

values and tracking changes in CO after therapeutic interventions in children was not true. We concluded that there was an unacceptable lack of agreement between the two technologies for measurement of CO in critically ill children. In addition, PRAM was also not able to track changes in CO accurately as compared to the TPUD method. The results were demonstrated by use of Bland-Altman and polar plot analysis. The study led to the revision of the PRAM algorithm, which requires further validation.
(Br J Anaesth. 2013 Mar;110(3):425-31).

Chapter 6 is a study of static and dynamic markers measured by TPUD and PRAM respectively for prediction of fluid responsiveness in the paediatric age group. Fluid overload is shown to be an independent risk factor for poor outcomes in critically ill patients. Only 50% of the ITU patients are known to be responders to fluid bolus administration leading to unnecessary fluid overload in the non-responders. Hence, administration of fluid boluses to likely responders will prevent fluid overload in predicted non-responder population. Our hypothesis regarding the predictive ability of novel static and dynamic markers measured by TPUD and PRAM respectively was false. The overall predictive ability for all the markers was poor . Volumetric (static) markers (ACVI, TEDVI and CBVI) measured by TPUD performed slightly better than the dynamic markers measured by PRAM (SVV, PV and SPV). TEDVI was the best predictor in our study.
However, baseline myocardial contractility had a significant influence on the stroke volume response after fluid bolus administration (true hypothesis). In addition, predictive ability improved slightly when baseline contractility was taken into account.
Search for newer, accurate markers and on going testing of accuracy of the established markers in different clinical settings for prediction of fluid responsiveness should continue. Effect of various elements of venous properties such as venous capacitance or resistance on stroke volume response to fluid bolus administration needs further investigation in children.

Chapter 7 is an observational, double blind study investigating the accuracy of TPUD for detection of small anatomic shunts. The accuracy was assessed against trans-thoracic echocardiography performed by experienced cardiologists as a reference method. The overall accuracy was 86.1% with a sensitivity of 85.7% and a specificity of 86.4%. The quantitative

estimation of ratio between pulmonary to systemic flow was also consistent with the echocardiographic findings on colour flow Doppler. We concluded that TPUD was qualitatively and quantitatively accurate method for detection of small anatomical shunts proving our hypothesis true.

(J Clin Monit Comput. 2015; 29(3):407-414)

Appendix

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Children/Young People INFORMATION SHEET

Advanced haemodynamic monitoring in critically ill children

We are asking if you would like to join in our research project. This sheet explains the research. We have given another sheet to your mum or dad, and we will be asking their permission, as well as yours.

What is research?

Research is how doctors and nurses find out the best way to look after children (and adults) when they get sick. For example, if we have a new medicine, we will compare the new medicine to an older one, to see which works best.

What is this research project about?

As you know, you will soon be having a heart operation. After the operation, you will be looked after in the PICU (this stands for: Paediatric Intensive Care Unit). You will have a chance to visit the PICU before your operation, and the nurses will explain how everything works.

After your operation, we will use special heart monitors to measure how fast your heart is beating and also what your blood pressure is.

Here's the research bit. We have two new types of heart monitor that we would like to use, as well as the ordinary monitors. We think that they may give us extra information that may be useful for children in the future who need heart operations.

What do I have to do?

You won't need to do anything. If you take part, we will use the two extra monitors, as well as the usual ones. The extra monitors connect to the usual ones, so you won't notice them.

Is it painful? Is it risky?

No. We won't need to do anything painful (like extra blood tests). The way we look after you will be exactly the same whether you take part in the research project or not.

Do I have to take part?

No, it's up to you and your mum or dad. If you want to take part, we will ask mum or dad to sign a form, giving us their permission.

Can I change my mind?

Yes, that's no problem if you do.

What happens after that?

If the monitors are useful, we will tell other doctors around the world.

What if I have some more questions?

Tell you mum or dad. They will get in contact with us (we are the doctors who are running the research project), and one of us can come and talk to you.

Our names are: Shane, Rohit and Naga.

Thanks for reading this!

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Parent/Guardian INFORMATION SHEET : Emergency Admissions

Advanced haemodynamic monitoring in critically ill children

We would like to invite you to allow your child to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. One of our research team members will be available to answer any questions you may have.

The study will look at **Advanced haemodynamic monitoring in critically ill children**

What is the purpose of the study?

When a child is admitted to the intensive care unit, they require very close monitoring. We routinely monitor heart rate and blood pressure, to allow us to assess how the heart and blood vessels (cardiovascular system) are functioning. In addition, depending upon the severity of the illness of your child, we may place additional lines into one of each type of the large blood vessels, called arteries and veins (arteries take blood out from heart to the different parts of the body, veins take blood from the rest of the body towards the heart). This allows us to monitor the cardiovascular system accurately and continuously.

In adults, it is possible to make a more detailed assessment of the cardiovascular system using extra monitoring equipment (for example, we can measure how much blood is being pumped around the body each minute). Up until now, these extra measurements have been very difficult to perform in children; one of the main limiting factors has been size. However, recent advances in technology means that monitors are now available which may be suitable for children.

In this study, we wish to evaluate two new cardiovascular monitors in ill children admitted to intensive care unit. We plan to use these monitors in addition to the routine measurements and monitoring. We will compare the information from the new monitors to that provided by our standard ones; however the new monitors will not be used to alter the type of care we give.

If these monitors provide useful new information, they may be used in the future to guide clinical care. For example, we may be able to better judge when a child needs fluid therapy, or to adjust the dose of medications used to support the heart and circulation.

Why have I been invited?

Your child has been invited because he/she has been admitted to intensive care and requires detailed monitoring using the lines described above. We aim to assess the new monitors in 100 children requiring intensive care.

Do I have to take part?

It is up to you to decide to join the study. If you do decide to enter your child into the study, you will be given this information sheet and a consent form to sign (for which you will receive a copy). Should you decide not to take part, the treatment of your child will not be affected. You are free to withdraw at any time, without giving a reason. However, if you do withdraw, we would ask that we can use the information that has already been collected.

What is involved in taking part?

Your child will be monitored in the intensive care unit with two extra monitors for up to 48 hours after admission.

One of the monitors, called PRAM (Pressure Related Analytical Method) does not actually attach onto your child directly, but uses information continuously taken from the routine blood pressure (arterial) line, which will have been placed earlier for standard care. The monitor is approximately 15" by 8", and will be placed behind the bed space.

The second monitor, is called 'COstatus™, (9" by 6" in size), and is used to measure blood flow with ultrasound technology. Here, we will make use of the two pressure monitoring lines that are already in place (one is arterial, for measuring blood pressure; the other is venous for measuring pressure in the veins). We will make a maximum of eight measurements over the 48 hours after admission. Each measurement takes approximately 5 minutes, and involves two steps. First, we will divert a small amount of blood (one teaspoon) from the blood pressure (arterial) line into the venous line. Second, we will inject a small amount of salt solution (saline) into the diversion, and the machine will then measure how the ultrasound signal changes during this process. The saline solution is exactly the same as that which we use as our intravenous fluids (in other words, your child will already be receiving saline as part of routine care). During measurement, we aim to recycle all of the blood back into your child's veins; very occasionally up to half a teaspoon may remain in the lines after the a set of measurement.

Are there any risks or side effects involved in taking part?

We do not foresee any risk with the PRAM monitor.

The second monitor (COstatus™) poses two potential risks:

First, as stated above, measurements may mean that a small amount of blood is withdrawn from your child. In majority of the cases, all of this blood is recycled back into your child's vein. However, very infrequently a small amount of this blood may be unsuitable for recycling .We anticipate that this may be up to a maximum of half a teaspoon per set of measurement, or a maximum of 2 teaspoons over 48 hours. This is extremely unlikely to have any consequence; for example this will not result in your child requiring a blood transfusion.

Second, when we make the measurements, we will be unable to use the arterial line to measure blood pressure for a period of approximately 10 seconds. If necessary, we can measure blood pressure during this time by other means. In addition, all other monitors will continue (heart rate, oxygen levels, breathing rate).

Your child will not experience any pain, as no needles are involved

Is there any benefit from being in the study?

No, there is no benefit to your child from taking part in this study. However, if we find an unexpectedly abnormal result, we will tell the clinical team looking after your child, who may perform extra tests to confirm this. For example, they may request an extra heart ultrasound scan

Who is performing the study?

The research is being led by Dr Shane Tibby who is a consultant in Paediatric intensive care. The research project is being undertaken as part of a higher degree (MD) for Dr Rohit Saxena (research fellow working in the intensive care unit).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee. This study has been reviewed and given favourable opinion by the South East London (2) Research Ethics Committee.

What happens with the results of the study?

Once we have collected all the information, we will analyse the data and then aim to publish these results within the following year in a medical journal. All information collected will be confidential, and no information will appear in any medical publication that will allow your child to be identified.

We can arrange to send you an electronic copy of the publication. Please mention your interest about this to a member of the research team so that your name and mailing details can be registered.

Is any payment involved?

The doctors involved will receive no payment for recruiting patients or performing the study. You or your child will not receive any payment if you decide to take part.

Who can I contact for further information?

If you have any concerns or questions about the study please contact:

i) Dr Shane Tibby, Consultant PICU, Evelina Children's Hospital
Contactable during weekdays on 020 7188 4572

ii) Dr Rohit Saxena, Clinical Research fellow, PICU, Evelina Children's Hospital. Tel 07940039078

iii) Dr Naga Kishore Puppala, Clinical Research fellow, PICU, Evelina Children's Hospital. Tel 07725056466

For out of hours queries, please contact a member of the medical team, who will relay this to the Consultant on call.

Thank you for considering your child taking part in the study. If you decide to take part, you will receive a copy of this information sheet and a copy of the signed consent form.

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CONSENT FORM

Title of Project: Advanced haemodynamic monitoring in critically ill children

Name of Principal Researcher: Dr Shane Tibby

Patient Identification Number for this trial: ☐

Please initial box

1. I confirm that I have read and understand the information sheet dated …… (version…….) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw him/her at any time, without giving any reason, without affecting his/her medical care or legal rights. ☐

3. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by responsible individuals from the research group where it is relevant to my child taking part in this research. I give permission for these individuals to have access to these records. ☐

4. I agree for my child to take part in the above study. ☐

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_____

Name of Child (Patient)

_____ _____

_____

Name of Parent / Guardian Date Signature

_____ _____

_____

Name of Person taking consent Date Signature

When completed, make three copies. Please retain the original and insert in the medical notes, give one copy to the patient's parent/guardian, and the final copy to the research team.

Thank You